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METHOD OF USING A COX-2 INHIBITOR AND A TOPOISOMERASE II INHIBITOR AS A COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA

FIELD OF THE INVENTION

[0001] The present invention relates to compositions and methods for the treatment, prevention or inhibition of a neoplasia or a neoplasia-related disorder in a mammal using a combination of a COX-2 inhibitor and a topoisomerase II inhibitor.

BACKGROUND OF THE INVENTION

[0002] Cancer is now the second leading cause of death in the United States and over 8,000,000 persons in the United States have been diagnosed with cancer. In 1995, cancer accounted for 23.3% of all deaths in the United States. (See U.S. Dept. of Health and Human Services, National Center for Health Statistics, Health United States 1996-97 and Injury Chartbook 117 (1997)).

[0003] Cancer is not fully understood on the molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene". Suppressive genes are growth regulatory genes, which upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called proto-oncogenes) that by mutation or altered context of expression become transforming genes. The products of transforming genes cause inappropriate cell growth. More than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content, cytoskeletal structure, protein secretion, gene expression and mortality (transformed cells can grow indefinitely).

[0004] A neoplasm, or tumor, is an abnormal, unregulated, and disorganized proliferation of cell growth, and is generally referred to as cancer. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness and metastasis. Invasiveness refers to the local spread of a neoplasm by infiltration or destruction of surrounding tissue, typically breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphotics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance.

[0005] Cancer is now primarily treated with one or a combination of three types of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, and skin, it cannot be used in the treatment of tumors located in other areas, such as the backbone, nor in the treatment of disseminated neoplastic conditions such as leukemia. Radiation therapy involves the exposure of living tissue to ionizing radiation causing death or damage to the exposed cells. Side effects from radiation therapy may be acute and temporary, while others may be irreversible. Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, lung, and testicular cancer.

[0006] The adverse effects of systemic chemotherapy used in the treatment of neoplastic disease are most feared by patients undergoing treatment for cancer. Of these adverse

effects nausea and vomiting are the most common and severe side effects. Other adverse side effects include cytopenia, infection, cachexia, mucositis in patients receiving high doses of chemotherapy with bone marrow rescue or radiation therapy; alopecia (hair loss); cutaneous complications (see M.D. Abeloff et al., Alopecia and Cutaneous Complications, p. 755-56 in Abeloff, M.D., Armitage, J.O., Lichter, A.S., and Niederhuber, J.E. (eds), Clinical Oncology, Churchill Livingston, New York, 1992, for cutaneous reactions to chemotherapy agents), such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving radiation or chemotherapy; and reproductive and endocrine complications. Chemotherapy-induced side effects significantly impact the quality of life of the patient and may dramatically influence patient compliance with treatment.

[0007] Additionally, adverse side effects associated with chemotherapeutic agents are generally the major dose-limiting toxicity (DLT) in the administration of these drugs. For example, mucositis, is one of the major dose limiting toxicity for several anticancer agents, including the antimetabolite cytotoxic agents 5-FU, methotrexate, and antitumor antibiotics, such as doxorubicin. Many of these chemotherapy-induced side effects if severe, may lead to hospitalization, or require treatment with analgesics for the treatment of pain.

[0008] Adverse side effects induced by anticancer therapy have become of major importance to the clinical management of cancer patients undergoing treatment for cancer or neoplasia disease.

[0009] Prostaglandins are arachidonate metabolites that are produced in virtually all mammalian tissues and possess diverse biologic capabilities, including vasoconstriction, vasodilation, stimulation or inhibition of platelet

aggregation, and immunomodulation, primarily immunosuppression. They are implicated in the promotion of development and growth of malignant tumors (Honn et al., Prostaglandins, 21, 833-64 (1981); Furuta et al., Cancer Res., 48, 3002-7 (1988); Taketo, J. Natl. Cancer Inst., 90, 1609-20 (1998)). They are also involved in the response of tumor and normal tissues to cytotoxic agents such as ionizing radiation (Milas and Hanson, Eur. J. Cancer, 31A, 1580-5 (1995)). Prostaglandin production is mediated by two cyclooxygenase enzymes, COX-1 and COX-2. Cyclooxygenase-1 (COX-1) is constitutively expressed and is ubiquitous. Cyclooxygenase-2 (COX-2) is induced by diverse inflammatory stimuli (Isakson et al., Adv. Pros. Throm. Leuk Res., 23, 49-54 (1995)).

[0010] Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) non-selectively inhibit both cyclooxygenase enzymes and consequently can prevent, inhibit, or abolish the effects of prostaglandins. Increasing evidence shows that NSAIDs can inhibit the development of cancer in both experimental animals and in humans, can reduce the size of established tumors, and can increase the efficacy of cytotoxic cancer chemotherapeutic agents.

[0011] Investigations have demonstrated that indomethacin prolongs tumor growth delay and increases the tumor cure rate in mice after radiotherapy (Milas et al., Cancer Res., 50, 4473-7, 1990). The influence of oxyphenylbutazone and radiation therapy on cervical cancer has been studied (Weppelmann and Monkemeier, Gyn. Onc., 17(2), 196-9 (1984)). However, treatment with NSAIDs is limited by toxicity to normal tissue, particularly by ulcerations and bleeding in the gastrointestinal tract, ascribed to the inhibition of COX-1. Recently developed selective COX-2 inhibitors exert potent anti-inflammatory activity but cause fewer side effects.

[0012] COX-2 has been linked to all stages of carcinogenesis (S. Gately, Cancer Metastasis Rev., 19(1/2),

19-27 (2000)). Recent studies have shown that compounds which preferentially inhibit COX-2 relative to COX-1 restore apoptosis and inhibit cancer cell proliferation (E. Fosslien, Crit. Rev. Clin. Lab. Sci., 37(5), 431-502 (2000)). COX-2 inhibitors, such as celecoxib, are showing promise for the treatment and prevention of colon cancer (R. A. Gupta et al., Ann. N. Y. Acad. Sci., 910, 196-206 (2000)) and in animal models for the treatment and prevention of breast cancer (L. R. Howe et al., Endocr.-Relat. Cancer, 8(2), 97-114 (2001)).

[0013] COX-2 inhibitors have been described for the treatment of cancer (WO 98/16227). COX-2 inhibitors have also been described for the treatment of tumors (EP 927,555). Celecoxib, an anti-inflammatory drug showing a high degree of selectivity for COX-2, exerted potent inhibition of fibroblast growth factor-induced corneal angiogenesis in rats (Masferrer et al., Proc. Am. Assoc. Cancer Research, 40, 396 (1999)).

[0014] Topoisomerase II inhibitors are one major class of chemotherapeutic agents (T. R. Toonen, *et al.*, Cancer Chemother. Biol. Response Modif., 19, 129-147 (2001)). Topoisomerase II inhibitors poison the enzyme by stimulating topoisomerase II DNA cleavage (D.A. Burden, *et al.*, Biophysica Acta, 1400, 139-154 (1998)). Examples of topoisomerase II inhibitors which are useful drugs for cancer treatment include, etoposide, teniposide, doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone (K. R. Hande, Biochim. Biophys. Acta, 1400, 173-184 (1998)). The use of epirubicin to treat breast cancer (D. Ormrod, *et al.*, Drugs Aging, 15(5), 389-416 (1999)) and bladder cancer (S.V. Onrust, *et al.*, Drugs Aging, 15(4), 307-333 (1999)) has been reviewed.

[0015] Myelosuppression, nausea and vomiting, and hair loss are common side effects for topoisomerase II inhibitors. The topoisomerase inhibitors etoposide and teniposide may also cause the development of acute non-lymphocytic leukemia. The anthracycline topoisomerase II inhibitors, along with

mitoxantrone, have a side effect of cardiac toxicity. Dexrazoxane has been developed as a cardioprotective agent for use in conjunction with anthracyclines, such as doxorubicin (C. Monneret, Eur. J. Med. Chem., 36, 484-493 (2001)).

[0016] WO 98/16227 describes the use of COX-2 inhibitors in the treatment or prevention of neoplasia.

[0017] WO 98/41511 describes 5-(4-sulphonylphenyl)-pyridazinone COX-2 inhibitors used for treating cancer.

[0018] WO 98/41516 describes (methylsulphonyl)phenyl-2-(5H)-furanone COX-2 inhibitors that can be used in the treatment of cancer.

[0019] U.S. Patent No. 6,294,558 describes tetracyclic sulfonylbenzene COX-2 inhibitors that may be used for the treatment of cancer.

[0020] WO 99/35130 describes 2,3-substituted indole COX-2 inhibitors that may be used for the treatment of cancer.

[0021] U.S. Patent No. 6,277,878 describes 2,3-substituted indole COX-2 inhibitors that may be used for the treatment of cancer.

[0022] WO 98/47890 describes substituted benzopyran derivatives that may be used alone or in combination with other active principles for the treatment of neoplasia.

[0023] WO 96/41645 describes a combination comprising a COX-2 inhibitor and a leukotriene A hydrolase inhibitor.

[0024] WO 97/11701 describes a combination comprising a COX-2 inhibitor and a leukotriene B4 receptor antagonist useful in treating colorectal cancer.

[0025] WO 97/29774 describes the combination of a COX-2 inhibitor and prostaglandin or antiulcer agent useful in treating cancer.

[0026] WO 97/36497 describes a combination comprising a COX-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer.

[0027] WO 99/18960 describes a combination comprising a COX-2 inhibitor and an induced nitric-oxide synthase inhibitor (iNOS) that can be used to treat colorectal and breast cancer.

[0028] WO 99/25382 describes compositions containing a COX-2 inhibitor and a N-methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases.

SUMMARY OF THE INVENTION

[0029] Among its several embodiments, the present invention provides a composition comprising an amount of a COX-2 inhibitor compound source and an amount of a topoisomerase II inhibitor wherein the amount of the COX-2 inhibitor compound source and the amount of the topoisomerase II inhibitor together comprise a therapeutically effective amount for the treatment, prevention, or inhibition of neoplasia or a neoplasia-related disorder, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0030] In another embodiment, the present invention further provides a combination therapy method for the treatment, prevention, or inhibition of neoplasia or a neoplasia-related disorder in a mammal in need thereof, comprising administering to the mammal an amount of a COX-2 inhibitor compound source and an amount of a topoisomerase II inhibitor wherein the amount of the COX-2 inhibitor compound source and the amount of the topoisomerase II inhibitor together comprise a therapeutically effective amount for the treatment, prevention, or inhibition of neoplasia or a neoplasia-related disorder, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0031] In still another embodiment, the present invention provides a pharmaceutical composition comprising an amount of a COX-2 inhibitor compound source and an amount of a

topoisomerase II inhibitor and a pharmaceutically-acceptable excipient, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0032] In yet another embodiment, the present invention further provides a kit that is suitable for use in the treatment, prevention or inhibition of a neoplasia or a neoplasia-related disorder, wherein the kit comprises a first dosage form comprising a COX-2 inhibitor compound source and a second dosage form comprising a topoisomerase II inhibitor, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention or inhibition of a neoplasia or a neoplasia-related disorder, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0033] Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0034] The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

[0035] The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

Definitions

[0036] The following definitions are provided in order to aid the reader in understanding the detailed description of the present invention.

[0037] The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0038] The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

[0039] The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred

alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0040] The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0041] The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

[0042] The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0043] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0044] The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[0045] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl,

cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[0046] The term "heterocyclo" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclo radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclo radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[0047] The term "heteroaryl" embraces unsaturated heterocyclo radicals. Examples of unsaturated heterocyclo radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclo group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing

1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic: group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclo radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, benzopyran, and the like. Said "heterocyclo group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[0048] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[0049] The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl"

radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[0050] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals.

[0051] The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH_2O_2S-.

[0052] The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and trifluoroacetyl.

[0053] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[0054] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO_2H. The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower

carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[0055] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[0056] The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[0057] The term "heterocycloalkyl" embraces saturated and partially unsaturated heterocyclo-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroarylsubstituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

[0058] The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an

oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical.

[0059] The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups that have been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups that have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[0060] The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "aminocarbonylalkyl"

denotes a carbonylalkyl group that has been substituted with an amino radical on the carbonyl carbon atom.

[0061] The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[0062] A component of the combination of the present invention is a cycloxygenase-2 selective inhibitor. The terms "cyclooxygenase-2 selective inhibitor," or "COX-2 selective inhibitor," which can be used interchangeably herein, embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds. In practice, the selectivity of a COX-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a COX-2 inhibitor can be measured as a ratio of the *in vitro* or *ex vivo* IC_{50} value for inhibition of COX-1, divided by the IC_{50} value for inhibition of COX-2 (COX-1 IC_{50}/COX-2 IC_{50}), or as a ratio of the *in vivo* ED_{50} value for inhibition of COX-1, divided by the ED_{50} value for inhibition of COX-2 (COX-1 ED_{50}/COX-2 ED_{50}). A COX-2 selective inhibitor is any inhibitor for which the ratio of COX-1 IC_{50} to COX-2 IC_{50}, or the ratio of COX-1 ED_{50} to COX-2 ED_{50}, is greater than 1. It is preferred that the ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100. As used herein, the terms "IC_{50}" and "ED_{50}" refer to the concentration of a compound

that is required to produce 50% inhibition of cyclooxygenase activity in an *in vitro* or *in vivo* test, respectively. Preferred COX-2 selective inhibitors of the present invention have a COX-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM. Preferred COX-2 selective inhibitors have a COX-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

[0063] The phrase "combination therapy" (or "co-therapy") embraces the administration of a COX-2 inhibiting agent and a topoisomerase II inhibitor as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a

fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients (such as, but not limited to, an antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

[0064] The phrase "therapeutically effective" is intended to qualify the amount of inhibitors in the therapy. This amount will achieve the goal of treating, preventing or inhibiting neoplasia or a neoplasia-related disorder.

[0065] "Therapeutic compound" means a compound useful in the treatment, prevention or inhibition of neoplasia or a neoplasia-related disorder.

[0066] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0067] The term "comprising" means "including the following elements but not excluding others."

Combinations and Methods

[0068] Among its several embodiments, the present invention provides a composition comprising an amount of a COX-2 inhibitor compound source and an amount of a topoisomerase II inhibitor wherein the amount of the COX-2 inhibitor compound source and the amount of the topoisomerase II inhibitor together comprise a therapeutically effective

amount for the treatment, prevention, or inhibition of neoplasia or a neoplasia-related disorder, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0069] In one embodiment, the source of the COX-2 inhibitor compound is a COX-2 inhibitor.

[0070] In another embodiment, the COX-2 inhibitor is a COX-2 selective inhibitor.

[0071] In another embodiment, the source of the COX-2 inhibitor compound is a prodrug of a COX-2 inhibitor compound, illustrated herein with parecoxib.

[0072] In another embodiment, the present invention further provides a combination therapy method for the treatment, prevention, or inhibition of neoplasia or a neoplasia-related disorder in a mammal in need thereof, comprising administering to the mammal an amount of a COX-2 inhibitor compound source and an amount of a topoisomerase II inhibitor wherein the amount of the COX-2 inhibitor compound source and the amount of the topoisomerase II inhibitor together comprise a therapeutically effective amount for the treatment, prevention, or inhibition of neoplasia or a neoplasia-related disorder, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0073] In still another embodiment, the present invention provides a pharmaceutical composition comprising an amount of a COX-2 inhibitor compound source and an amount of a topoisomerase II inhibitor and a pharmaceutically-acceptable excipient, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0074] In yet another embodiment, the present invention further provides a kit that is suitable for use in the treatment, prevention or inhibition of a neoplasia or a

neoplasia-related disorder, wherein the kit comprises a first dosage form comprising a COX-2 inhibitor compound source and a second dosage form comprising a topoisomerase II inhibitor, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention or inhibition of a neoplasia or a neoplasia-related disorder, provided that the COX-2 inhibitor compound source is not a 2,3-substituted indole compound or a tetracyclic sulfonylbenzene compound.

[0075] The methods and compositions of the present invention provide one or more benefits. Combinations of COX-2 inhibitors with the compounds, compositions, agents and therapies of the present invention are useful in treating, preventing or inhibiting neoplasia or a neoplasia-related disorder. Preferably, the COX-2 inhibitors and the compounds, compositions, agents and therapies of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations.

[0076] The combinations of the present invention will have a number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the therapeutic compounds used in the combinations of the present invention will be lower than are typical for dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects of the individual therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater patient compliance with therapy regimens. Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

[0077] When administered as a combination, the therapeutic agents can be formulated as separate compositions

that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

[0078] There are many uses for the present inventive combination. For example, topoisomerase II inhibitors and COX-2 selective inhibiting agents (or prodrugs thereof) are each believed to be effective antineoplastic or antiangiogenic agents. However, patients treated with a topoisomerase II inhibitor frequently experience gastrointestinal side effects, such as nausea and diarrhea. The present inventive combination will allow the subject to be administered a topoisomerase II inhibitor at a therapeutically effective dose yet experience reduced or fewer symptoms of nausea and diarrhea. A further use and advantage is that the present inventive combination will allow therapeutically effective individual dose levels of the topoisomerase II inhibitor and the COX-2 inhibitor that are lower than the dose levels of each inhibitor when administered to the patient as a monotherapy.

[0079] Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the treatment, prevention or reduction of the risk of developing neoplasia disease may inhibit enzyme activity through a variety of mechanisms. By way of example, the cyclooxygenase inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme. The use of a COX-2 selective inhibiting agent is highly advantageous in that they minimize the gastric side effects that can occur with non-selective non-steroidal antiinflammatory drugs (NSAIDs), especially where prolonged treatment is expected.

[0080] Besides being useful for human treatment, these methods are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals,

rodents, avians, and the like. More preferred animals include horses, dogs, and cats.

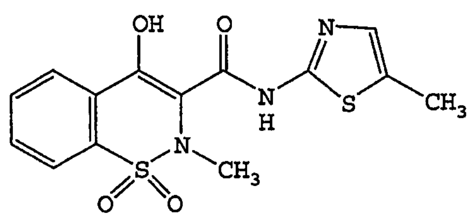
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[0081] A component of the combination of the present invention is a cycloxygenase-2 selective inhibitor. The terms "cyclooxygenase-2 selective inhibitor," or "Cox-2 selective inhibitor," which can be used interchangeably herein, embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds.

[0082] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100. As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM. Preferred cycloxoygenase-2 selective inhibitors have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

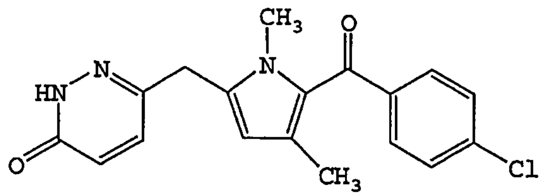
[0083] Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is parecoxib sodium. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598, which is hereby incorporated by reference in its entirety.

[0084] The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug of meloxicam.



B-1

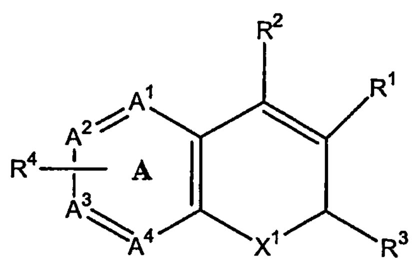
[0085] In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug of RS 57067.



B-2

[0086] In another embodiment of the invention the cyclooxygenase-2 selective inhibitor is of the chromene/chroman structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the compounds having a structure shown by general Formulas I, II, III, IV, V, and VI, shown below, and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs of the compounds disclosed in Table 1.

[0087] Benzopyrans that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent No. 6,271,253. One such class of compounds is defined by the general formula shown below in formulas **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1-C_3-alkyl, (optionally substituted phenyl)-C_1-C_3-alkyl, acyl and carboxy-C_1-C_6-alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1-C_3-alkyl, phenyl-C_1-C_3-alkyl, C_1-C_3-perfluoroalkyl, chloro, C_1-C_6-alkylthio, C_1-C_6-alkoxy, nitro, cyano and cyano-C_1-C_3-alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1-C_6-alkylsulfonylaminocarbonyl and C_1-C_6-alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1-C_6-alkyl and C_2-C_6-alkenyl;

wherein R^3 is selected from C_1-C_3-perfluoroalkyl, chloro, C_1-C_6-alkylthio, C_1-C_6-alkoxy, nitro, cyano and cyano-C_1-C_3-alkyl;

wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo-C_2-C_6-alkynyl, aryl-C_1-C_3-alkyl, aryl-C_2-C_6-alkynyl, aryl-C_2-C_6-alkenyl, C_1-C_6-alkoxy, methylenedioxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryl-C_1-C_6-alkyloxy, heteroaryl-C_1-C_6-alkyloxy, aryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-haloalkoxy, C_1-C_6-haloalkylthio, C_1-C_6-haloalkylsulfinyl, C_1-C_6-haloalkylsulfonyl, C_1-C_3-(haloalkyl-C_1-C_3-hydroxyalkyl, C_1-C_6-hydroxyalkyl, hydroxyimino-C_1-C_6-alkyl, C_1-C_6-alkylamino, arylamino, aryl-C_1-C_6-alkylamino, heteroarylamino, heteroaryl-C_1-C_6-alkylamino, nitro, cyano, amino, aminosulfonyl, C_1-C_6-alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1-C_6-alkylaminosulfonyl, heteroaryl-C_1-C_6-alkylaminosulfonyl, heterocyclylsulfonyl, C_1-C_6-alkylsulfonyl, aryl-C_1-C_6-alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1-C_6-alkylcarbonyl, heteroaryl-

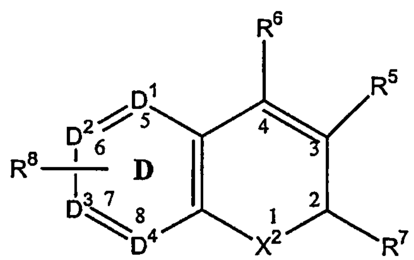
C_1-C_6-alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1-C_1-alkoxycarbonyl, formyl, C_1-C_6-haloalkylcarbonyl and C_1-C_6-alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt of a compound having formula I.

[0088] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes a compound having the structure of formula **II**:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1-C_3-alkyl, (optionally substituted phenyl) -C_1-C_3-alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1-C_6-alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1-C_3-alkyl, phenyl-C_1-C_3-alkyl, C_1-C_3-perfluoroalkyl, chloro, C_1-C_6-alkylthio, C_1-C_6-alkoxy, nitro, cyano and cyano-C_1-C_3-alkyl;

or wherein $CR^c R^b$ form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1-C_6-alkylsulfonylaminocarbonyl and C_1-C_6-alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2-C_6-alkynyl and C_2-C_6-alkenyl;

wherein R^7 is selected from C_1-C_3-perfluoroalkyl, chloro, C_1-C_6-alkylthio, C_1-C_6-alkoxy, nitro, cyano and cyano-C_1-C_3-alkyl;

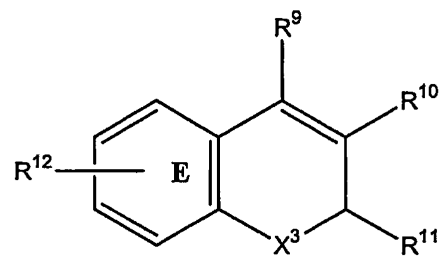
wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, halo-C_2-C_6-alkynyl, aryl-C_1-C_3-alkyl, aryl-C_2-C_6-alkynyl, aryl-C_2-C_6-alkenyl, C_1-C_6-alkoxy, methylenedioxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, $O(CF_2)_2O$—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryl-C_1-C_6-alkyloxy, heteroaryl-C_1-C_6-alkyloxy, aryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-haloalkoxy, C_1-C_6-haloalkylthio, C_1-C_6-haloalkylsulfinyl, C_1-C_6-haloalkylsulfonyl, C_1-C_3-(haloalkyl-C_1-C_3-hydroxyalkyl), C_1-C_6-hydroxyalkyl, hydroxyimino-C_1-C_6-alkyl, C_1-C_6-alkylamino, arylamino, aryl-C_1-C_6-alkylamino, heteroarylamino, heteroaryl-C_1-C_6-alkylamino, nitro, cyano, amino, aminosulfonyl, C_1-C_6-alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1-C_6-alkylaminosulfonyl, heteroaryl-C_1-C_6-alkylaminosulfonyl, heterocyclylsulfonyl, C_1-C_6-alkylsulfonyl, aryl-C_1-C_6-alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1-C_6-alkylcarbonyl, heteroaryl-C_1-C_6-alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1-C_6-alkoxycarbonyl, formyl, C_1-C_6-haloalkylcarbonyl and C_1-C_6-alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt of a compound having formula II.

[0089] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula **III**:

Formula III is:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^9 is selected from the group consisting of H and aryl;

wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

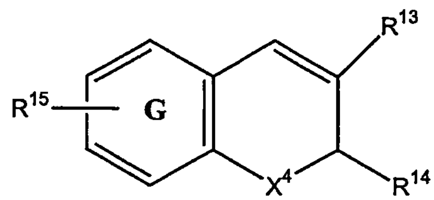
wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl,

aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt of a compound having formula III.

[0100] A related class of compounds useful as cyclooxygenase-2 selective inhibitors in the present invention is described by Formulas IV and V:



IV

wherein X^4 is selected from O or S or NR^a;

wherein R^a is alkyl;

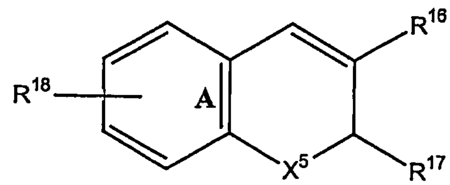
wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl; wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt of a compound having formula IV.

[0101] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt of a compound having formula V.

[0102] In yet another embodiment, the compound having formula **V** is:

wherein X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt of a compound having formula V.

[0103] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered

heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt of a compound having formula V.

[0104] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt of a compound having formula V.

[0105] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

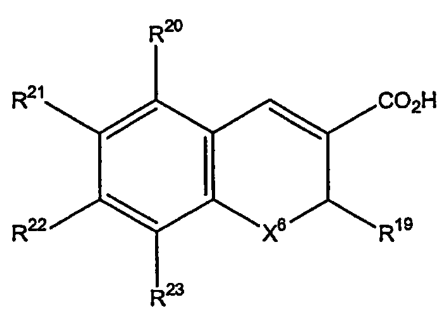
R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt of a compound having formula V.

[0106] The cyclooxygenase-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**, wherein:



VI

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or pharmaceutically acceptable salt of a compound having formula VI.

[0107] The cyclooxygenase-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

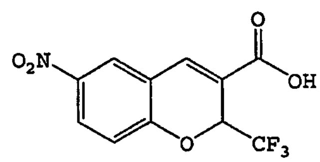
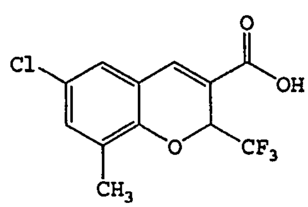
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

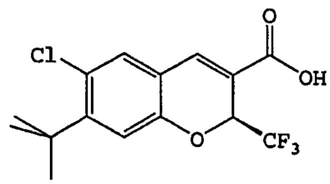
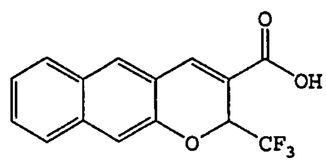
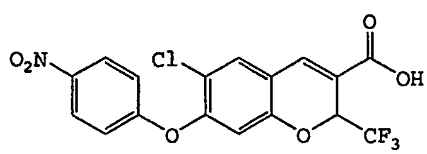
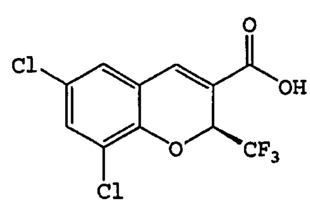
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

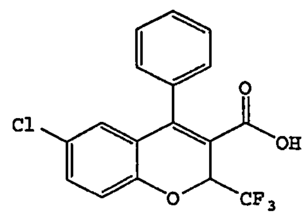
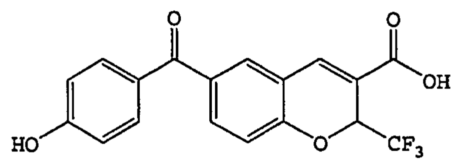
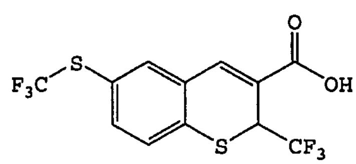
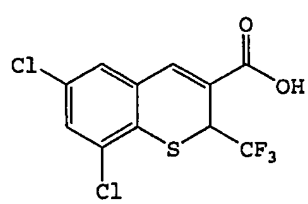
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

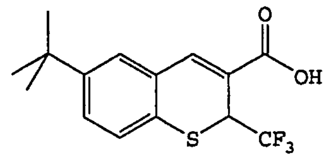
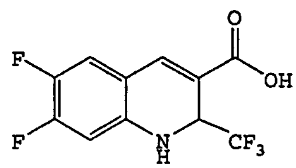
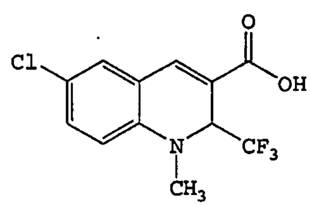
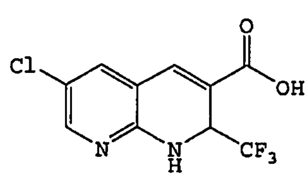
or an isomer or pharmaceutically acceptable salt of a compound having formula VI.

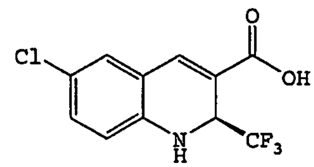
[0108] Table 1. Examples of Chromene Cox-2 Selective Inhibitors

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl) -2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid

Compound Number	Structural Formula
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

[0109] Examples of specific compounds that are useful for the cyclooxygenase-2 selective inhibitor include (without limitation):

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

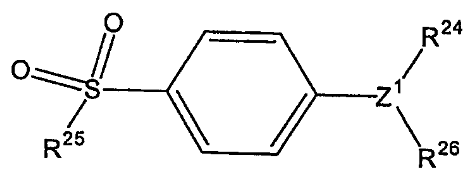
s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or an isomer of a compound listed above.

[0110] In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

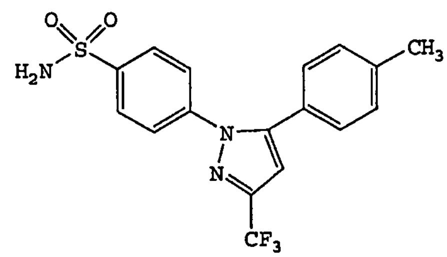
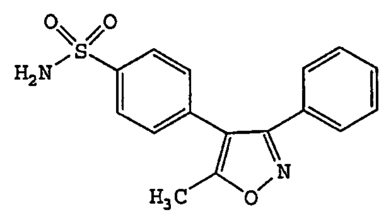
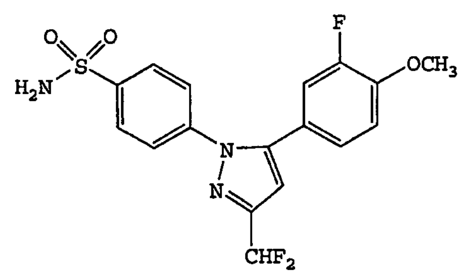
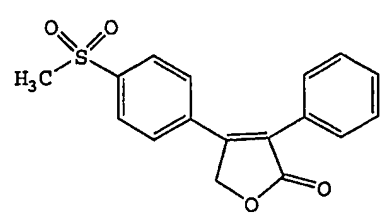
R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

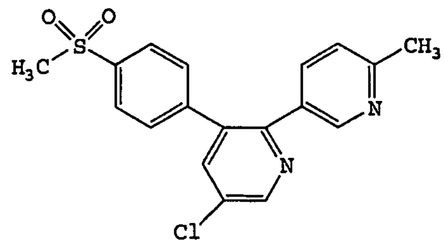
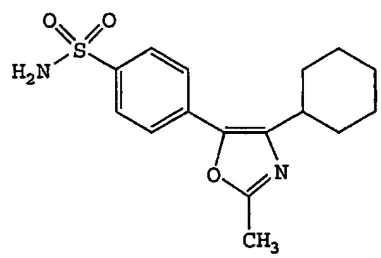
or a pharmaceutically acceptable salt or isomer of a compound having formula VII.

[0111] In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a prodrug thereof.

[0112] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

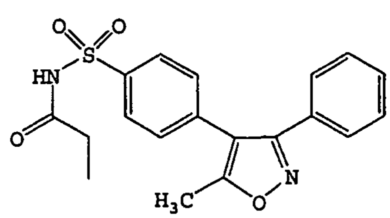
[0113] Table 2. Examples of Tricyclic COX-2 Selective Inhibitors

Compound Number	Structural Formula
B-18	
B-19	
B-20	
B-21	

Compound Number	Structural Formula
B-22	
B-23	

[0114] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

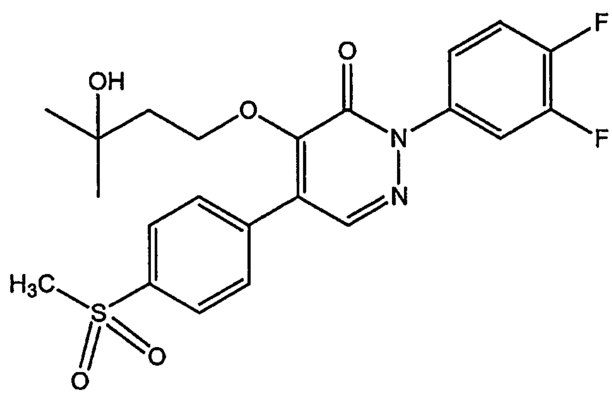
[0115] In a preferred embodiment of the invention, parecoxib (See, *e.g.* U.S. Patent No. 5,932,598), having the structure shown in B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, (See, *e.g.*, U.S. Patent No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor.



B-24

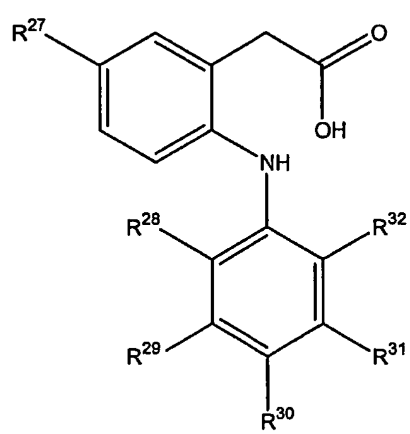
[0116] A preferred form of parecoxib is sodium parecoxib.

[0117] In another embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

[0118] In a yet further embodiment of the invention, the cyclooxygenase inhibitor used in connection with the methods of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula VIII:



VIII

or an isomer, or a pharmaceutically acceptable salt of a compound having formula VIII;
wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{31} and R^{32} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[0119] A phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in Formula VIII, wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[0120] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor is a compound that has the structure shown in Formula VIII,
wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[0121] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib), having CAS Reg. No. 220991-20-8, and having the structure shown in Formula VIII,

wherein:

R^{27} is methyl;

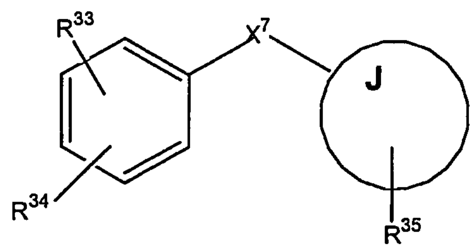
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[0122] Compounds that have a structure similar to that shown in Formula VIII, which can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,310,099, 6,291,523, and 5,958,978.

[0123] Other cyclooxygenase-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X^7 is O; J is 1-phenyl; $X_7R^{33}$is 2-$NHSO_2CH_3$; $R^{34}$is 4-NO_2; and there is no R^{35}group, (nimesulide), and

X^7 is O; J is 1-oxo-inden-5-yl; $R^{33}$is 2-F; $R^{34}$is 4-F; and $R^{35}$is 6-$NHSO_2CH_3$, (flosulide); and

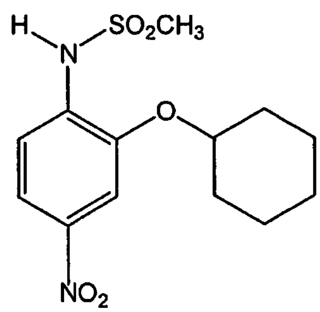
X^7 is O; J is cyclohexyl; $R^{33}$is 2-$NHSO_2CH_3$; $R^{34}$is 5-NO_2; and there is no R^{35}group, (NS-398); and

X^7 is S; J is 1-oxo-inden-5-yl; $R^{33}$is 2-F; $R^{34}$is 4-F; and $R^{35}$is 6-$N^-SO_2CH_3$ Na^+, (L-745337); and

X^7 is S; J is thiophen-2-yl; $R^{33}$is 4-F; there is no R^{34}group; and $R^{35}$is 5-$NHSO_2CH_3$,RWJ-63556); and

X^7 is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; $R^{33}$is 3-F; $R^{34}$is 4-F; and $R^{35}$is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

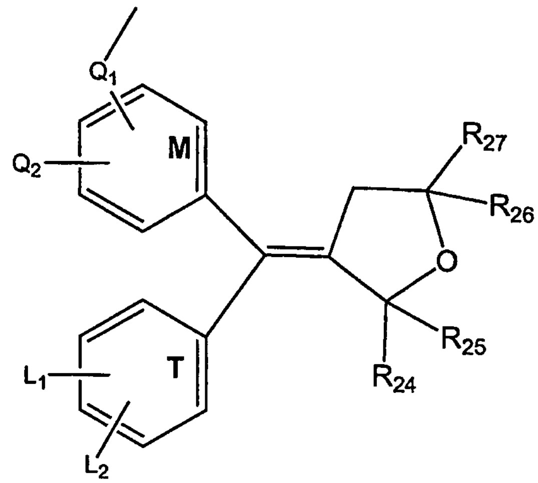
[0124] Further information on the applications of the Cox-2 selective inhibitor N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4)*:406- 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra*, available at: http://www.gbhap.com/Science-_Spectra/20-1-article.htm (06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol., 75(2)*:191- 194 (1997).



B-26

[0125] An evaluation of the anti-inflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[0126] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are:

a phenyl radical,

a naphthyl radical,

a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is:

an $-S(O)_n-R$ group, in which n is an integer equal to 0, 1 or 2 and R is:

a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having 1 to 6 carbon atoms, or

an $-SO_2NH_2$ group;

and is located in the para position,

the others independently being:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a trifluoromethyl radical, or

a lower O-alkyl radical having 1 to 6 carbon atoms, or

Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom, or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or.a pharmaceutically acceptable salt of a compound having formula X.

[0127] Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[0128] Cyclooxygenase-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-

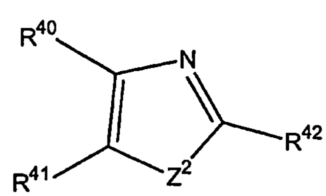
purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[0129] Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoinde derivative which has IC_{50} values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED_{50} = 0.39 mg/kg.

[0130] Compounds that may act as cyclooxygenase-2 selective inhibitors include multibinding compounds containing from 2 to 10 ligands covalently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[0131] Compounds that may act as cyclooxygenase-2 inhibitors include conjugated linoleic acid that is described in U.S. Patent No. 6,077,868.

[0132] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

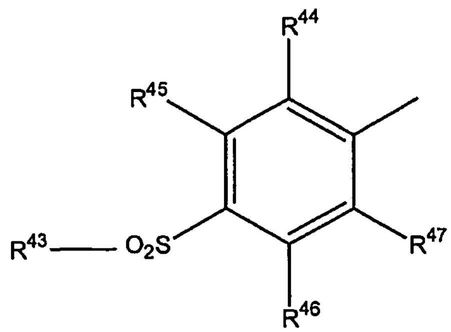


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



wherein:

R^{43} is lower alkyl, amino or lower alkylamino; and

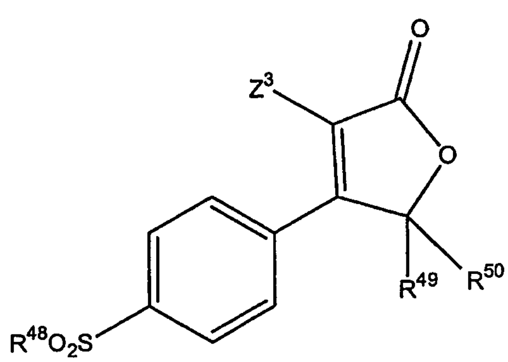
R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy or amino,

provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl,

and a pharmaceutically acceptable salt or an isomer of a compound having formula XI

[0133] Cox-2 selective inhibitors that are useful in the subject method and compositions can include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of:

linear or branched C_{1-6} alkyl,

(b) linear or branched C_{1-6} alkoxy,

(c) unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_{1-3} alkoxy,

(4) CN,

(5) C_{1-3} fluoroalkyl

(6) C_{1-3} alkyl,

(7) $-CO_2H$;

$R^{48}$is selected from the group consisting of NH_2 and CH_3,

$R^{49}$is selected from the group consisting of:

C_{1-6}alkyl unsubstituted or substituted with C_{3-6} cycloalkyl, and

C_{3-6}cycloalkyl;

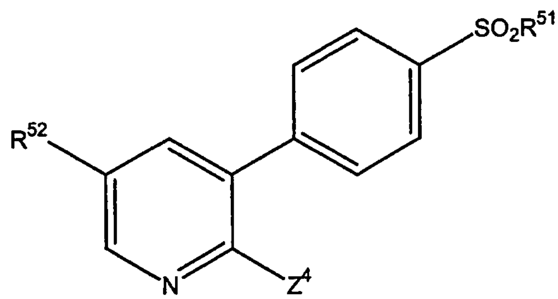
$R^{50}$is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with one, two or three fluoro atoms; and

C_{3-6} cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[0134] Materials that can serve as cyclooxygenase-2 selective inhibitors include pyridines that are described in U.S. Patent Nos. 6, 369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and which have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of:

(a) CH_3

(b) NH_2,

(c) $NHC(O)CF_3$,

(d) $NHCH_3$;

Z^4 is a mono-, di-, or tri-substituted phenyl or pyridinyl (or the N-oxide thereof),

wherein the substituents are chosen from the group consisting of:

(a) hydrogen,

(b) halo,

(c) C_{1-6} alkoxy,

(d) C_{1-6} alkylthio,

(e) CN,

(f) C_{1-6} alkyl,

(g) C_{1-6} fluoroalkyl,

(h) N_3,

(i) $-CO_2R^{53}$,

(j) hydroxy,

(k) $-C(R^{54})(R^{55})-OH$,

(l) $-C_{1-6}alkyl-CO_2-R^{56}$,

(m) C_{1-6}fluoroalkoxy;

R^{52} is chosen from the group consisting of:

(a) halo,

(b) C_{1-6}alkoxy,

(c) C_{1-6} alkylthio,

(d) CN,

(e) C_{1-6} alkyl,

(f) C_{1-6} fluoroalkyl,

(g) N_3,

(h) $-CO_2R^{57}$,

(i) hydroxy,

(j) $-C(R^{58})(R^{59})-OH$,

(k) $-C_{1-6}alkyl-CO_2-R^{60}$,

(l) C_{1-6}fluoroalkoxy,

(m) NO_2,

(n) $NR^{61}R^{62}$, and

(o) $NHCOR^{63}$;

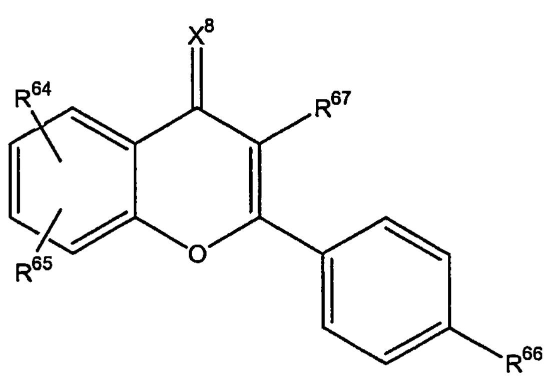
R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, are each independently chosen from the group consisting of:

hydrogen, and

C_{1-6}alkyl;

or R^{54} and R^{55}, R^{58} and R^{59} or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[0135] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

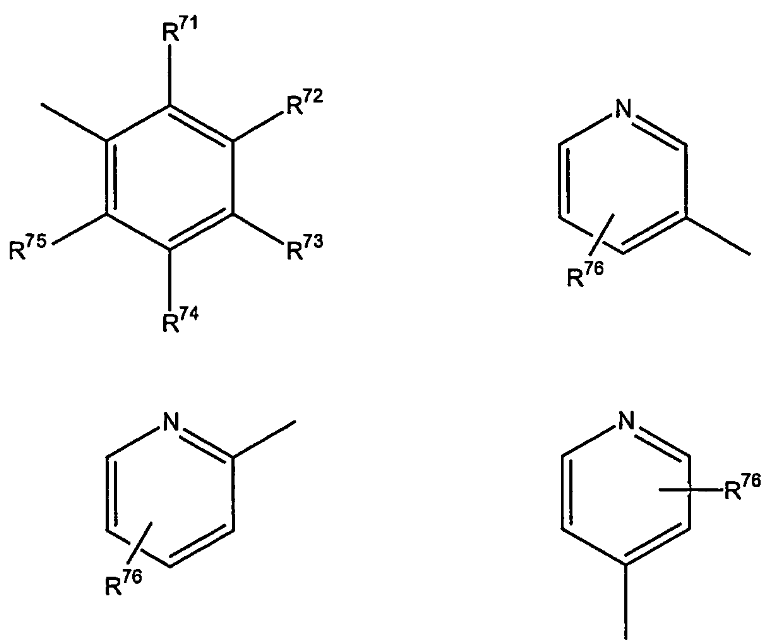
wherein:

X^8 is an oxygen atom or a sulfur atom;

R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1-C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0-2, R^{68} is a hydrogen atom, a C_1-C_6 lower alkyl group, or a group of a formula: $NR^{69}R^{70}$ wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1-C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1-C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:



wherein:

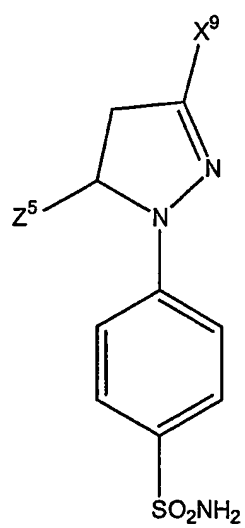
R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a

C_1-C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: $NR^{69}R^{70}$, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1-C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

[0136] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:

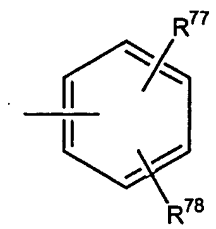


XV

wherein:

X^9 is selected from the group consisting of C_1-C_6 trihalomethyl, preferably trifluoromethyl; C_1-C_6alkyl; and an

optionally substituted or di-substituted phenyl group of formula **XVI**:



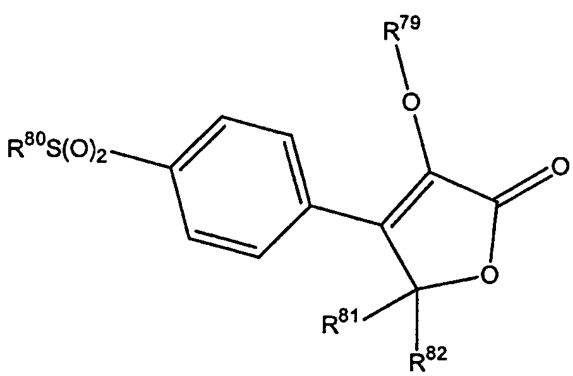
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1-C_6alkyl, preferably C_1-C_3 alkyl; C_1-C_6 alkoxy, preferably C_1-C_3 alkoxy; carboxy; C_1-C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[0137] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

R^{79} is a mono-, di-, or tri-substituted C_{1-12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_{3-12} cycloalkenyl, or an unsubstituted or mono, di- or tri-substituted C_{5-12} cycloalkynyl, wherein the substituents are chosen from the group consisting of:

(a) halo, selected from F, Cl, Br, and I,

(b) OH,

(c) CF_3,

(d) C_{3-6} cycloalkyl,

(e) =O,

(f) dioxolane,

(g) CN; and

R^{80} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$,

(d) $NHCH_3$;

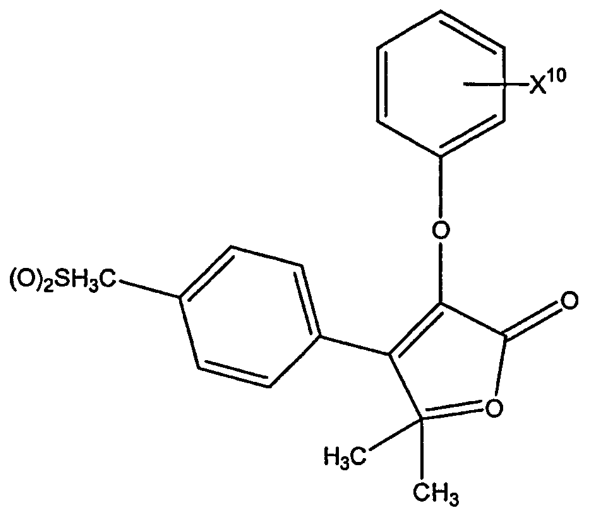
R^{81} and R^{82} are independently chosen from the group consisting of:

(a) hydrogen,

(b) C_{1-10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

[0138] In another embodiment the cyclooxygenase-2 selective inhibitor may be a compound having formula **XVIII**:

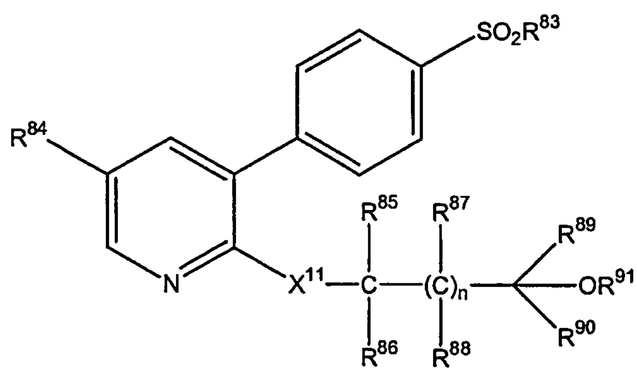


XVIII

wherein:

X^{10} is fluoro or chloro.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

wherein:

X^{11} is selected from the group consisting of:

(a) O,

(b) S,

(c) bond;

n is 0 or 1;

R^{83} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$;

R^{84} is chosen from the group consisting of:

(a) halo,

(b) C_{1-6} alkoxy,

(c) C_{1-6} alkylthio,

(d) CN,

(e) C_{1-6} alkyl,

(f) C_{1-6} fluoroalkyl,

(g) N_3,

(h) $—CO_2\ R^{92}$,

(i) hydroxy,

(j) $—C(R^{93})(R^{94})—OH$,

(k) $—C_{1-6}$ alkyl-CO_2 $—R^{95}$,

(l) C_{1-6} fluoroalkoxy,

(m) NO_2,

(n) $NR^{96}\ R^{97}$,

(o) $NHCOR^{98}$;

R^{85} to R^{98} are independently chosen from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl;

or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond, and a pharmaceutically acceptable salt or an isomer of a compound having formula XIX.

One preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is a bond.

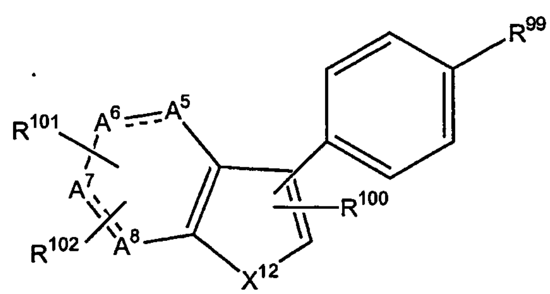
Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is O.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is S.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{83} is CH_3.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{84} is halo or C_{1-6} fluoroalkyl.

[0139] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:

$-A^5=A^6-A^7=A^8-$ is selected from the group consisting of:

(a) $-CH=CH-CH=CH-$,

(b) $-CH_2-CH_2-CH_2-C(O)-$, $-CH_2-CH_2-C(O)-CH_2-$, $-CH_2-C(O)-CH_2-CH_2$, $-C(O)-CH_2-CH_2-CH_2$,

(c) $-CH_2-CH_2-C(O)-$, $-CH_2-C(O)-CH_2-$, $-C(O)-CH_2-CH_2-$

(d) $-CH_2-CH_2-O-C(O)-$, $CH_2-O-C(O)-CH_2-$, $-O-C(O)-CH_2-CH_2-$,

(e) $-CH_2-CH_2-C(O)-O-$, $-CH_2-C(O)-OCH_2-$, $-C(O)-O-CH_2-CH_2-$,

(f) $-C(R^{105})_2-O-C(O)-$, $-C(O)-O-C(R^{105})_2-$, $-O-C(O)-C(R^{105})_2-$, $-C(R^{105})_2-C(O)-O-$,

(g) $-N=CH-CH=CH-$,

(h) $-CH=N-CH=CH-$,

(i) $-CH=CH-N=CH-$,

(j) $-CH=CH-CH=N-$,

(k) $-N=CH-CH=N-$,

(l) $-N=CH-N=CH-$,

(m) $-CH=N-CH=N-$,

(n) $-S-CH=N-$,

(o) $-S-N=CH-$,

(p) $-N=N-NH-$,

(q) $-CH=N-S-$, and

(r) $-N=CH-S-$;

R^{99} is selected from the group consisting of:

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

(c) $S(O)_2NHCOCF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHCOCF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_{1-6}alkyl,

(b) C_{3-7},cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_{1-6}alkoxy,

(4) C_{1-6}alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6}alkyl,

(8) N_3,

(9) $-CO_2H$,

(10) $-CO_2-C_{1-4}$alkyl,

(11) $-C(R^{103})(R^{104})-OH$,

(12) $-C(R^{103})(R^{104})-O-C_{1-4}$alkyl, and

(13) $-C_{1-6}$alkyl-CO_2-R^{106};

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) $-C(R^{103})(R^{104})-OH$, and

(10) $-C(R^{103})(R^{104})-O-C_{1-4}$ alkyl;

(11) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of $-A^5=A^6-A^7=A^8-$ and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) $-Q^3$ wherein Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$,

(f) $-O-Q^4$,

(g) $-S-Q^4$, and

(h) optionally substituted:

(1) $-C_{1-5}$ alkyl-Q^3,

(2) $-O-C_{1-5}$ alkyl-Q^3,

(3) $-S-C_{1-5}$ alkyl-Q^3,

(4) $-C_{1-3}$ alkyl-$O-C_{1-3}$ alkyl-Q^3,

(5) $-C_{1-3}$ alkyl-$S-C_{1-3}$ alkyl-Q^3,

(6) $-C_{1-5}$ alkyl-$O-Q^4$,

(7) $-C_{1-5}$ alkyl-$S-Q^4$,

wherein the substituent resides on the alkyl chain and the substituent is C_{1-3} alkyl, and Q^3 is Q^4, CO_2H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2-C_{1-4} alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O-C_{1-4}$ alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl; or

R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_{1-6} alkyl;

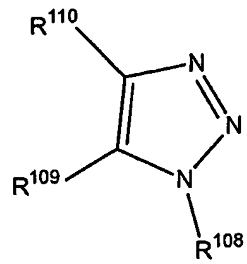
R^{107} is hydrogen, C_{1-6} alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, $-C(R^{107})=C(R^{107})-$; $-C(R^{107})=N-$;

$-N=C(R^{107})-$.

Compounds that may act as cyclooxygenase-2 inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No.

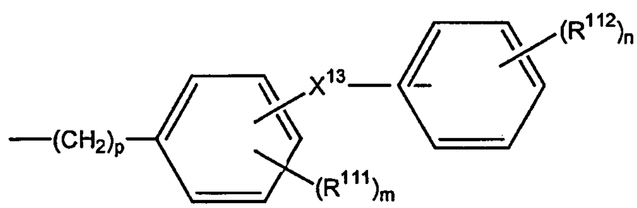
6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

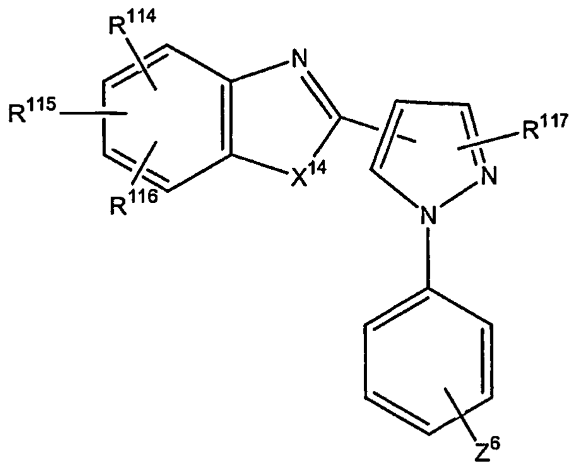
R^{108} is:



wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5; X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or C=NR^{113} where R^{113} is hydrogen, lower alkyl, hydroxy, lower alkoxy, amino, lower alkylamino, diloweralkylamino or cyano; and, R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, lower alkanoyl, nitro, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, trifuloromethoxy, acetamido, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R^{109} is amino, mono or diloweralkylamino, acetamido, acetimido, ureido, formamido, formamido or guanidino; and R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the lower alkyl, lower alkyl containing, lower alkoxy and lower alkanoyl groups contain from 1 to 3 carbon atoms.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyrazole derivatives that are described in U.S. Patent 6,136,831. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen, R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or lower alkanoyloxy;

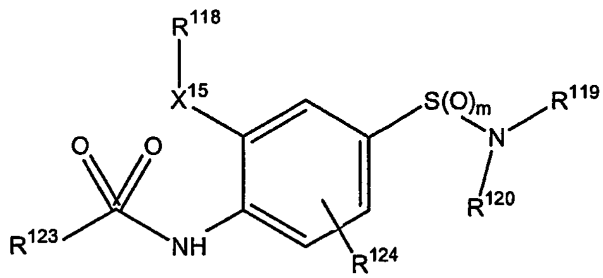
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable saltor an isomer of a compound having formula XXII.

[0140] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$–X^{16};

X^{16} denotes halogen, NO_2, $-OR^{121}$, $-COR^{121}$, $-CO_2R^{121}$, $-OCO_2R^{121}$, $-CN$, $-CONR^{121}OR^{122}$, $-CONR^{121}R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2$;

R^{121}, $-NR^{121}$ R^{122}, $-NHC(O)R^{121}$, $-NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C- atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

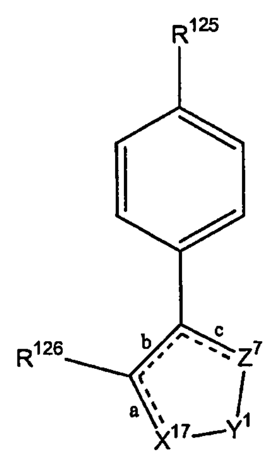
R^{124} denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, $-OR^{121}$, $-COR^{121}$, $-CO_2R^{121}$, $-OCO_2R^{121}$, $-CN$, $-CONR^{121}OR^{122}$, $-CONR^{121}R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2R^{121}$, $-NR^{121}R^{122}$, $-NHC(O)R^{121}$, $-NHS(O)_2R^{121}$, or a polyfluoroalkyl group;

R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable saltsor isomer of a compound.having formula XXIII.

[0141] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones that are described in U.S. Patent 6,239,173. Such 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones have the formula shown below in formula **XXIV**:



XXIV

wherein:

$X^{17}-Y^{1}-Z^{7}$-is selected from the group consisting of:

(a) $-CH_2CH_2CH_2-$,

(b) $-C(O)CH_2CH_2-$,

(c) $-CH_2CH_2C(O)-$,

(d) $-CR^{129}(R^{129'})-O-C(O)-$,

(e) $-C(O)-O-CR^{129}(R^{129'})-$,

(f) $-CH_2-NR^{127}-CH_2-$,

(g) $-CR^{129}(R^{129'})-NR^{127}-C(O)-$,

(h) $-CR^{128}=CR^{128'}-S-$,

(i) $-S-CR^{128}=CR^{128'}-$,

(j) $-S-N=CH-$,

(k) $-CH=N-S-$,

(l) $-N=CR^{128}-O-$,

(m) $-O-CR4=N-$,

(n) $-N=CR^{128}-NH-$,

(o) $-N=CR^{128}-S-$, and

(p) $-S-CR^{128}=N-$,

(q) $-C(O)-NR^{127}-CR^{129}(R^{129'})-$,

(r) $-R^{127}N-CH=CH-$ provided R_{122} is not $-S(O)_2CH_3$,

(s) $-CH=CH-NR^{127}$ – provided R^{125} is not $-S(O)_2CH_3$,

when side b is a double bond, and sides a and c are single bonds; and in another embodiment

$X^{17}-Y^1-Z^7$-is selected from the group consisting of:

(a) $=CH-O-CH=$, and

(b) $=CH-NR^{127}-CH=$,

(c) $=N-S-CH=$,

(d) $=CH-S-N=$,

(e) $=N-O-CH=$,

(f) $=CH-O-N=$,

(g) $=N-S-N=$,

(h) $=N-O-N=$,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

(c) $S(O)_2NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_{1-6} alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl,

wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_{1-6} alkoxy,

(4) C_{1-6} alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6} alkyl,

(8) N_3,

(9) $-CO_2H$,

(10) $-CO_2-C_{1-4}$ alkyl,

(11) $-C(R^{129})(R^{130})-OH$,

(12) $-C(R^{129})(R^{130})-O-C_{1-4}$ alkyl, and

(13) $-C_{1-6}$ alkyl-CO_2-R^{129} ;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) $-C(R^{129})(R^{130})-OH$, and

(10) $-C(R^{129})(R^{130})-O-C_{1-4}$ alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) hydroxyC_{1-6} alkyl,

(f) $-C(O)-C_{1-6}$ alkyl,

(g) optionally substituted:

(1) $-C_{1-5}$ alkyl-Q^5,

(2) $-C_{1-3}$ alkyl-O$-C_{1-3}$ alkyl-Q^5,

(3) $-C_{1-3}$ alkyl-S$-C_{1-3}$ alkyl-Q^5,

(4) $-C_{1-5}$ alkyl-O$-Q^5$, or

(5) $-C_{1-5}$ alkyl-S$-Q^5$,

wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl;

(h) $-Q^5$;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) $-Q^5$,

(f) $-O-Q^5$;

(g) $-S-Q^5$, and

(h) optionally substituted:

(1) $-C_{1-5}$ alkyl-Q^5,

(2) $-O-C_{1-5}$ alkyl-Q^5,

(3) $-S-C_{1-5}$ alkyl-Q^5,

(4) $-C_{1-3}$ alkyl-$O-C_{1-3}$ alkyl-Q^5,

(5) $-C_{1-3}$ alkyl-$S-C_{1-3}$ alkyl-Q^5,

(6) $-C_{1-5}$ alkyl-$O-Q^5$,

(7) $-C_{1-5}$ alkyl-$S-Q^5$,

wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

(b) C_{1-6} alkyl;

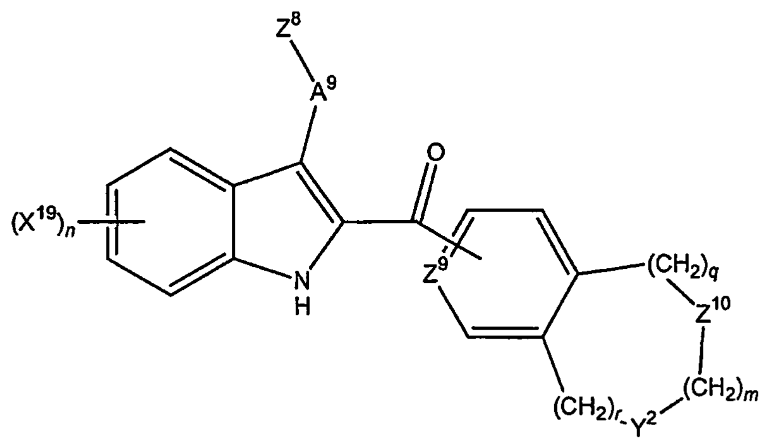
or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2 H, CO_2 $-C_{1-4}$ alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or

$C(R^{131})(R^{132})(O-C_{1-4}$ alkyl);

provided that when X—Y—Z is $-S-CR^{128}=CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[0142] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bicycliccarbonyl indole compounds that are described in U.S. Patent No. 6,303,628. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

wherein:

A^9 is C_{1-6} alkylene or $-NR^{133}-$;

Z^8 is $C(=L^3)R^{134}$, or SO_2 R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from $-CH_2-$, O, S and $-N-R^{133}$;

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

R^{133} is hydrogen or C_{1-4} alkyl;

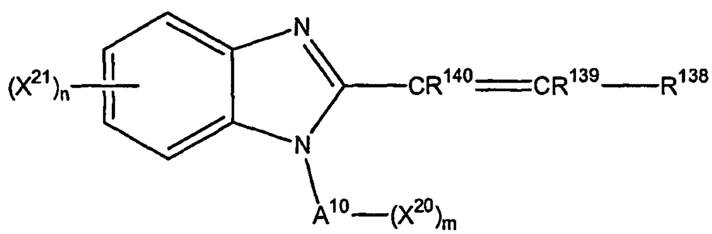
R^{134} is hydroxy, C_{1-6} alkyl, halo-substituted C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkyl(C_{3-7} cycloalkoxy), $-NR^{136}R^{137}$, C_{1-4} alkylphenyl-O– or phenyl-O–, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy and nitro;

R^{135} is C_{1-6} alkyl or halo-substituted C_{1-6} alkyl;

and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and halo-substituted C_{1-6} alkyl, or an isomer or pharmaceutically acceptable salt of a compound having formula XXV.

[0143] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

wherein:

A^{10} is heteroaryl selected from

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkyl, hydroxy-substituted C_1-C_4 alkyl, (C_1-C_4 alkoxy)C_1-C_4 alkyl, halo-substituted C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino, N, N-di(C_1-C_4 alkyl)amino, [N-(C_1-C_4 alkyl)amino]C_1-C_4 alkyl, [N, N-di(C_1-C_4 alkyl)amino]C_1-C_4 alkyl, N-(C_1-C_4 alkanoyl)amonio, N-

(C_1-C_4 alkyl)(C_1-C_4 alkanoyl)amino, N-[(C_1-C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1-C_4 alkyl)sulfonyl]amino, C_1-C_4 alkanoyl, carboxy, (C_1-C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1-C_4 alkyl)amino]carbonyl, [N, N-di(C_1-C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1-C_4 alkyl)thio, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1-C_4 alkyl)amino]sulfonyl and [N, N-di(C_1-C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkyl, hydroxy-substituted C_1-C_4 alkyl, (C_1-C_4 alkoxy)C_1-C_4 alkyl, halo-substituted C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino, N, N-di(C_1-C_4 alkyl)amino, [N-(C_1-C_4 alkyl)amino]C_1-C_4 alkyl, [N, N-di(C_1-C_4 alkyl)amino]C_1-C_4 alkyl, N-(C_1-C_4 alkanoyl)amino, N-(C_1-C_4 alkyl)-N-(C_1-C_4 alkanoyl) amino, N-[(C_1-C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1-C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1-C_4 alkoxy)cabonyl, cabamoyl, [N-(C_1-C_4 alkyl) amino]carbonyl, [N, N-di(C_1-C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1-C_4 alkyl)thio, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1-C_4 alkyl)amino]sulfonyl and [N, N-di(C_1-C_4 alkyl)amino]sulfonyl;

R^{138} is selected from hydrogen, straight or branched C_1-C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo hydroxy, C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino and N, N-di(C_1-C_4 alkyl)amino, C_3-C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino and N, N-di(C_1-C_4 alkyl)amino, C_4-C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, amino, N-(C_1-C_4

alkyl)amino and N, N-di(C_1-C_4 alkyl)amino, phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, halo-substituted C_1-C_4 alkyl, hydroxy-substituted C_1-C_4 alkyl, (C_1-C_4 alkoxy)C_1-C_4 alkyl, halo-substituted C_1-C_4 alkoxy, amino, N- (C_1-C_4 alkyl)amino, N, N-di(C_1-C_4 alkyl)amino, [N-(C_1-C_4 alkyl)amino]C_1-C_4 alkyl, [N, N-di(C_1-C_4 alkyl)amino]C_1-C_4 alkyl, N-(C_1-C_4 alkanoyl)amino, N-[C_1-C_4 alkyl)(C_1-C_4 alkanoyl)]amino, N-[(C_1-C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1-C_4 alkyl)sulfonyl]amino, C_1-C_4 alkanoyl, carboxy, (C_1-C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1-C_4 alky)amino]carbonyl, [N, N-di(C_1-C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1-C_4 alkyl)thio, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1-C_4 alkyl)amino]sulfonyl and [N, N-di(C_1-C_4 alkyl)amino]sulfonyl; and heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from:

hydrogen,

halo,

C_1-C_4 alkyl,

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, amino, N-(C_1-C_4 alkyl)amino and N, N-di(C_1-C_4 alkyl)amino,

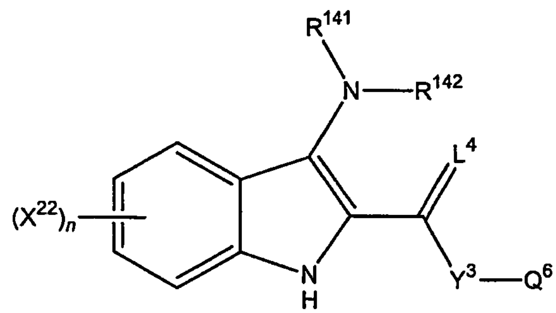
or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3-C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4;

or an isomer or pharmaceuitcally acceptable salt of a compound having formula XXVI.

[0144] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_{1-4} alkylidene;

Q^6 is:

(a) C_{1-6} alkyl or halosubstituted C_{1-6} alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkoxy, amino and mono- or di-(C_{1-4} alkyl)amino,

(b) C_{3-7} cycloalkyl optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, $S(O)_mR^{143}$, SO_2

NH_2, $SO_2N(C_{1-4}$ alkyl$)_2$, amino, mono- or di-(C_{1-4}alkyl)amino, $NHSO_2R^{143}$, NHC(O)R^{143}, CN, CO_2H, $CO_2(C_{1-4}$ alkyl), C_{1-4} alkyl-OH, C_{1-4} alkyl-OR^{143}, $CONH_2$, CONH(C_{1-4} alkyl), CON(C_{1-4} alkyl$)_2$ and –O–Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_{1-4} alkyl, CF_3, hydroxy, OR^{143}, $S(O)_mR^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substitutents independently selected from: (d-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, C_{1-4} alkyl-OH, $S(O)_m$ R^{143}, SO_2 NH_2, SO_2 N(C_{1-4} alkyl$)_2$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2$ R^{143}, NHC(O)R^{143}, CN, CO_2 H, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OR^{143}, $CONH_2$, CONH(C_{1-4} alkyl), CON(C_{1-4} alkyl$)_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, OCF_3, SR^{143}, SO_2 CH_3, SO_2 NH_2, amino, C_{1-4} alkylamino and $NHSO_2$ R^{143};

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_{1-6} alkyl optionally substituted with a substituent selected independently from hydroxy, OR^{143}, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2 H, CO_2 (C_{1-4} alkyl), $CONH_2$, CONH(C_{1-4} alkyl) and CON(C_{1-4} alkyl$)_2$;

R^{142} is:

(a) hydrogen,

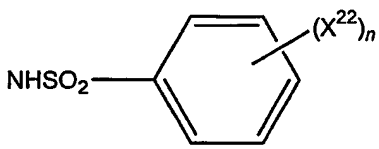
(b) C_{1-4} alkyl,

(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_{1-22} alkyl or C_{2-22} alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:

(c-1-1) halo, hydroxy, OR^{143}, $S(O)_m R^{143}$, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $CO_2 H$, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulae:



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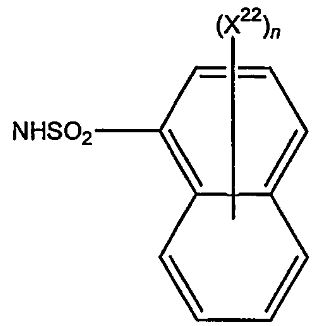

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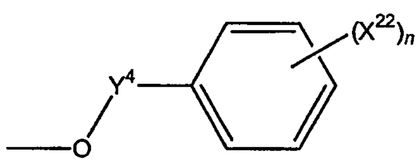

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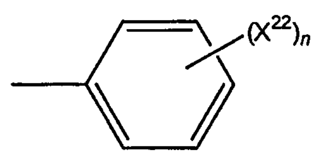

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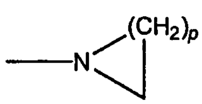

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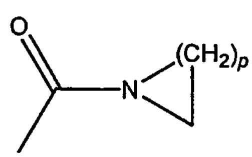

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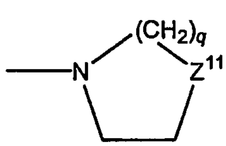

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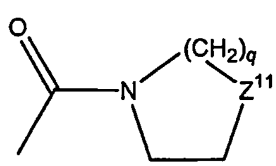


(c-2) C_{1-22} alkyl or C_{2-22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

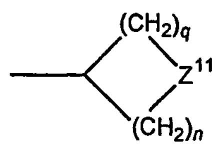
(c-3) $-Y^5-C_{3-7}$ cycloalkyl or $-Y^5-C_{3-7}$ cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:
(c-3-1) C_{1-4} alkyl, hydroxy, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl$)_2$,

(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:
(c-4-1) halo, C_{1-8} alkyl, C_{1-4} alkyl-OH, hydroxy, C_{1-8} alkoxy, halosubstituted C_{1-8} alkyl, halosubstituted C_{1-8} alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_{1-4}$ alkyl), $SO_2 N(C_{1-4}$ alkyl$)_2$, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_{1-4} alkyl, hydroxy, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2H, CO_2 (C_{1-4} alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_{1-8} alkyl, C_{1-4} alkyl-OH, hydroxy, C_{1-8} alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, CO_2H and CO_2 (C_{1-4} alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2H, $CO_2(C_{1-4}$ alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl$)_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstitutued C_{1-4} alkoxy, $S(O)_mR^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2R^{143}$, nitro, halosubstitutued C_{1-4} alkyl, CN, CO_2H, $CO_2(C_{1-4}$ alkyl), C_{1-4} alkyl-OH, C_{1-4} alkylOR^{143}, $CONH_2$, CONH(C_{1-4} alkyl) or CON(C_{1-4} alkyl)$_2$;

R^{143} is C_{1-4} alkyl or halosubstituted C_{1-4} alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_{1-6} alkyl, halosubstitutued C_{1-4} alkyl or -Y^5-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, CF_3, OCF_3, CN and nitro;

with the proviso that a group of formula -Y^5–Q is not methyl or ethyl when X^{22} is hydrogen;

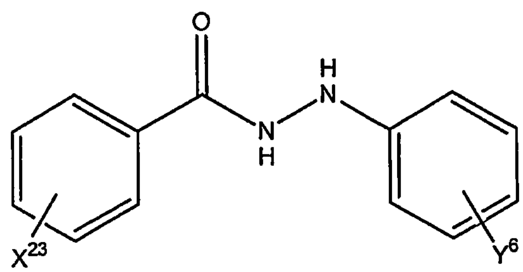
L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl;

or an isomer or a pharmaceutically acceptable sale of a compound having formula XXVII.

[0145] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII** or are pharmaceutically acceptable salts or isomers of compounds having formula XXVIII:

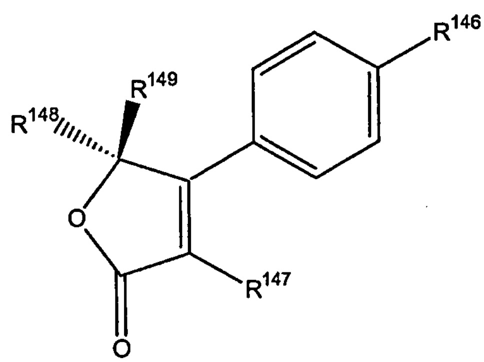


XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino or other oxygen and sulfur containing functional groups such as hydroxy, methoxy and methylsulfonyl.

[0146] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX** or are pharmaceutically acceptable salts or isomers of compounds having formula XXIX:



XXIX

wherein:

R^{146} is selected from the group consisting of SCH_3, $-S(O)_2CH_3$ and $-S(O)_2NH_2$;

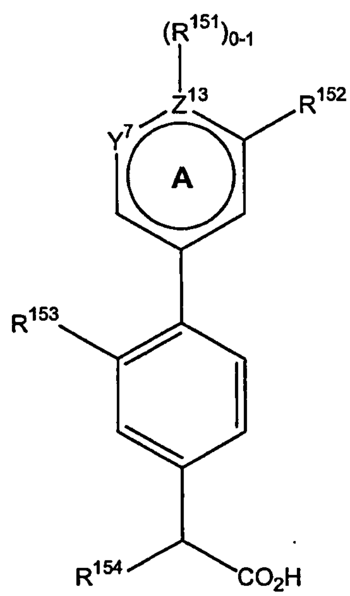
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_{1-4}alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[0147] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX** or are pharmaceutically acceptable salts or isomers of compounds having formula XXX:



XXX

wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an energetically stable configuration planar with ring A to within about 15 degrees;

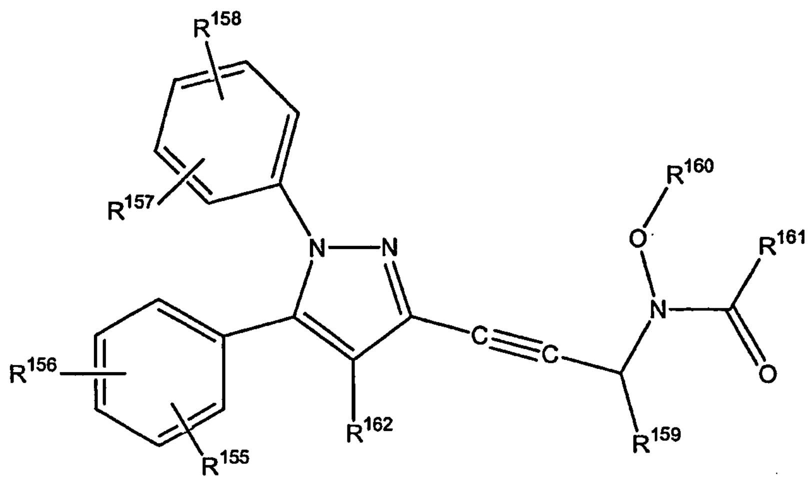
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_{1-2} alkyl, $-OC_{1-2}$ alkyl, $-NHC_{1-2}$ alkyl, $-N(C_{1-2}\text{ alkyl})_2$, $-C(O)C_{1-2}$ alkyl, $-S-C_{1-2}$ alkyl and $-C(S)C_{1-2}$ alkyl;

Y^7 represents N, CH or $C-OC_{1-3}$ alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[0148] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI** or are pharmaceutically acceptable salts or isomers of compounds having formula XXXI:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_{1-5} alkyl, C_{1-5} alkoxy, phenyl, halo, hydroxy, C_{1-5} alkylsulfonyl, C_{1-5} alkylthio, trihalo C_{1-5} alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_{1-5} alkyl, trihalo C_{1-5} alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

R^{160} is hydrogen, C_{1-5} alkyl, phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihalo C_{1-5} alkyl or nitro, or R^{160} is C_{1-5} alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihalo C_{1-5} alkyl or nitro;

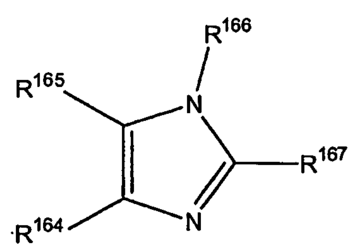
R^{161} is C_{1-10} alkyl, substituted C_{1-10} alkyl where the substituents are halogen, trihalo C_{1-5} alkyl, C_{1-5} alkoxy, carboxy, C_{1-5} alkoxycarbonyl, amino, C_{1-5} alkylamino, diC_{1-5} alkylamino, diC_{1-5} alkylaminoC_{1-5} alkylamino, C_{1-5} alkylaminoC_{1-5} alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_{1-5}

alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_{1-5} alkyl, halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

R^{161} is $NR^{163}R^{164}$ where R^{163} and R^{164} are independently selected from hydrogen and C_{1-5} alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_{1-5} alkyl;

R^{162} is hydrogen, C_{1-5} alkyl, nitro, amino, and halogen.

[0149] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII** or are pharmaceutically acceptable salts or isomers of compounds having formula XXXII:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl and halogen, or

substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, SEM, C_{1-5} alkoxycarbonyl, aryloxycarbonyl, arylC_{1-5} alkyloxycarbonyl, arylC_{1-5} alkyl, phthalimidoC_{1-5} alkyl, aminoC_{1-5} alkyl, diaminoC_{1-5} alkyl, succinimidoC_{1-5} alkyl, C_{1-5} alkylcarbonyl, arylcarbonyl, C_{1-5} alkylcarbonylC_{1-5} alkyl, aryloxycarbonylC_{1-5} alkyl, heteroarylC_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted arylC_{1-5} alkyl, wherein the aryl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, C_{1-5} alkoxy, halogen, amino, C_{1-5} alkylamino, and diC_{1-5} alkylamino;

R^{167} is $(A^{11})_n-(CH^{165})_q-X^{24}$ wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, phenoxy, phenyl, arylC_{1-5} alkyl, amino, C_{1-5} alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, araC_{1-5} alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine, substituted C_{1-5} alkyl,

wherein the substituents are selected from the group consisting of one or more C_{1-5} alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy, substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy, substituted C_{1-5} alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino, substituted arylC_{1-5} alkyl,

wherein the alkyl substituent is hydroxyl, substituted arylC_{1-5} alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy, substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, arylC_{1-5} alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted C_{1-5} alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,

substituted C_{1-5} alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_{1-5} alkoxy and trifluoromethyl, with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

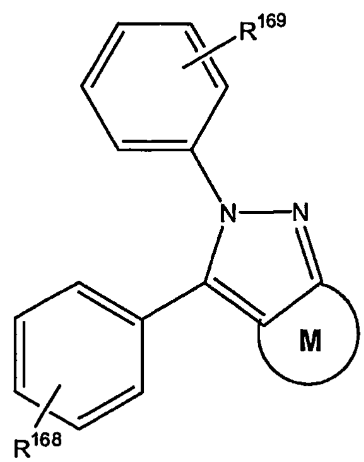
if A^{11} is sulfur and q is 1, then X^{24} cannot be C_{1-2} alkyl;

if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl,C_{1-5} alkylsulfonyl or phenylsulfonyl;

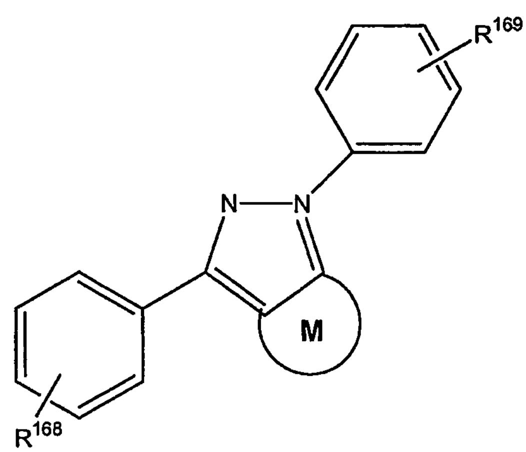
if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not SEM (2-(trimethylsilyl)ethoxymethyl);

if n is 0 and q is 0, then X^{24} cannot be hydrogen; and pharmaceutically acceptable salts thereof.

[0150] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



XXXIII

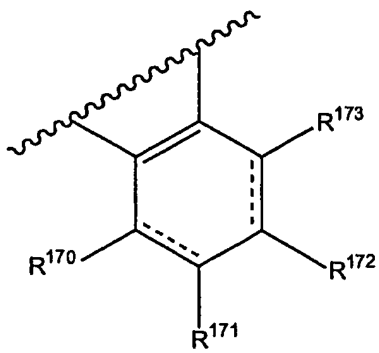


XXXIV

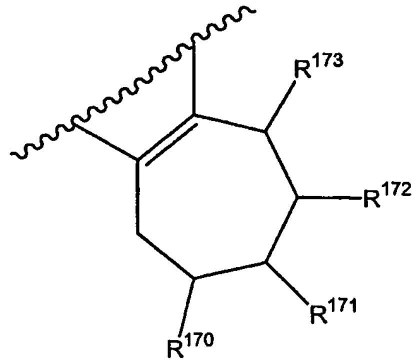
wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1-C_6)alkyl, $(C_1\ C_6)$alkoxy, nitro, amino, hydroxy, trifluoro, $-S(C_1-C_6)$alkyl, $-SO(C_1-C_6)$alkyl and $-SO_2\ (C_1-C_6)$alkyl; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



,or



wherein:

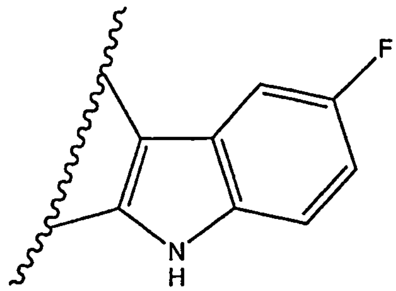
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxy and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of $-OCOCH_2-$, $-ONH(CH_3)COCH_2-$, $-OCOCH=$ and $-O-$;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, $=NOH$, $-NR^{174}R^{175}$, $-OCH_3$, $-OCH_2CH_3$, $-OSO_2NHCO_2CH_3$, $=CHCO_2CH_2$ CH_3, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2CON(CH_3)_2$, $-CH_2CO_2NHCH_3$, $-CHCHCO_2CH_2CH_3$, $-OCON(CH_3)OH$, $-C(COCH_3)_2$, di(C_1-C_6)alkyl and di(C_1-C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxy, amino, (C_1-C_6)alkyl and (C_1-C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of $-O-$ and

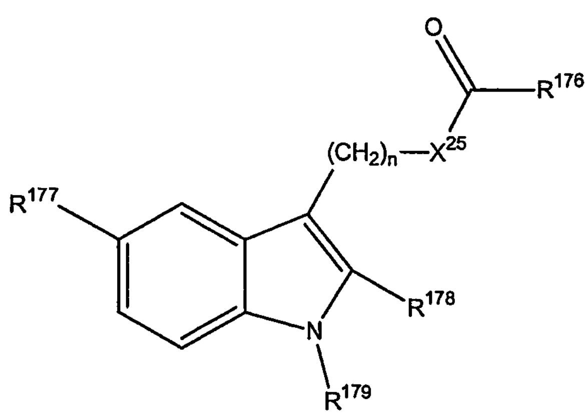


R^{174} is selected from the group consisting of hydrogen, OH, $-OCOCH_3$, $-COCH_3$ and (C_1-C_6)alkyl; and

R^{175} is selected from the group consisting of hydrogen, OH, $-OCOCH_3$, $-COCH_3$, (C_1-C_6)alkyl, $-CONH_2$ and $-SO_2CH_3$ with the proviso that if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts and isomers of compounds having formula XXXIII or XXXIV.

[0151] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_8 cycloalkyl, C_1 to C_6 hydroxyalkyl, branched C_1 to C_6 hydroxyalkyl, hydroxy substituted C_4 to C_8 aryl, primary, secondary or tertiary C_1 to C_6 alkylamino, primary, secondary or tertiary branched C_1 to C_6 alkylamino, primary, secondary or tertiary C_4 to C_8 arylamino, C_1 to C_6 alkylcarboxylic acid, branched C_1 to C_6 alkylcarboxylic acid, C_1 to C_6 alkylester, branched C_1 to C_6 alkylester, C_4 to C_8 aryl, C_4 to C_8 arylcarboxylic acid, C_4 to C_8 arylester, C_4 to C_8 aryl substituted C_1 to C_6 alkyl, C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_8 cycloalkyl, C_4 to C_8 aryl, C_4 to C_8 aryl-substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 branched alkoxy, C_4 to C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

R^{178} is hydrogen, C_1 to C_6 alkyl or C_1 to C_6 branched alkyl;

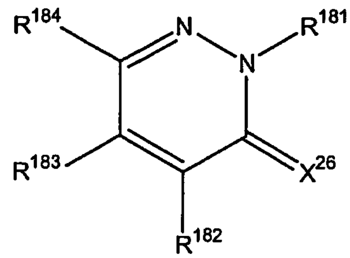
R^{179} is C_1 to C_6 alkyl, C_4 to C_8 aroyl, C_4 to C_8 aryl, C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 to C_8 aryl-substituted C_1 to C_6 alkyl, alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 to C_8 aroyl, or alkyl-substituted C_4 to C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N–R^{180}, where R^{180} is C_1 to C_6 alkyl or C_1 to C_6 branched alkyl.

[0152] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include

pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI** or are pharmaceutically acceptable salts or isomers of compounds having formula XXXVI:



XXXVI

wherein:

X^{26} is selected from the group consisting of O, S, $-NR^{185}$, $-NOR^{a}$, and $-NNR^{b}R^{c}$;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^{a}, R^{b}, and R^{c} are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, $-(CH_2)_nC(O)R^{186}$, $-(CH_2)_nCH(OH)R^{186}$, $-(CH_2)_nC(NOR^{d})R^{186}$, $-(CH_2)_nCH(NOR^{d})R^{186}$, $-(CH_2)_nCH(NR^{d}R^{e})R^{186}$, $-R^{187}R^{188}$, $-(CH_2)_nC{\equiv}CR^{188}$, $-(CH_2)_n[CH(CX^{26'}_3)]_m$

$(CH_2)_pR^{188}$, $-(CH_2)_n(CX^{26'}{}_2)_m$ $(CH_2)_pR^{188}$, and $-(CH_2)_n(CHX^{26'})_m$ $(CH_2)_mR^{188}$;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

n is an integer from 0-10; and

p is an integer from 0-10; and

R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:

wherein:

X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193} R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, $-NHNH_2$, and $-NCHN(R^{191})R^{192}$;

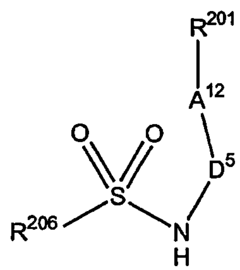
R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

Y^8 is selected from the group consisting of $-OR^{195}$, $-SR^{195}$, $-C(R^{197})(R^{198})R^{195}$, $-C(O)R^{195}$, $-C(O)OR^{195}$, $-N(R^{197})C(O)R^{195}$, $-NC(R^{197})R^{195}$, and $-N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[0153] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



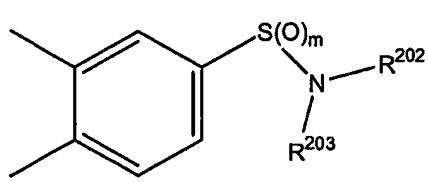
XXXVII

wherein:

A^{12} denotes oxygen, sulphur or NH;

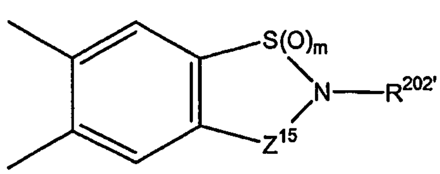
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n$-X^{29}; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n$-X^{29}, $R^{202'}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$-X^{29},

X^{29} denotes halogen, NO_2, $-OR^{204}$, $-COR^{204}$, $-CO_2R^{204}$, $-OCO_2R^{204}$, $-CN$, $-CONR^{204}OR^{205}$, $-CONR^{204}R^{205}$, $-SR^{204}$, $-S(O)R^{204}$, $-S(O)_2R^{204}$, $-NR^{204}R^{205}$, $-NHC(O)R^{204}$, $-NHS(O)_2R^{204}$;

Z^{15} denotes $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH{=}CH-$, $-CH{=}CH-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-$, $-NHCO-$, $-CONH-$, $-NHCH_2-$, $-CH_2NH-$, $-N{=}CH-$, $-NHCH-$, $-CH_2-CH_2-NH-$, $-CH{=}CH-$, $-N-R^{203}$, $-{=}O$, $-S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

R^{206} is a straight-chained or branched C_{1-4}-alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

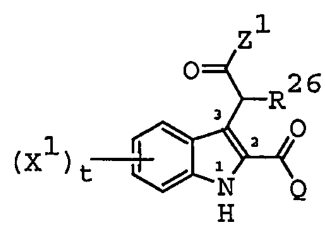
m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3 or a pharmaceutically acceptable salt or isomer of a compound having formula XXXVII.

[0154] COX-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent Nos. 6,169,188, 6,020,343, 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No.

6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent No. 6,359,182 (C-nitroso compounds).

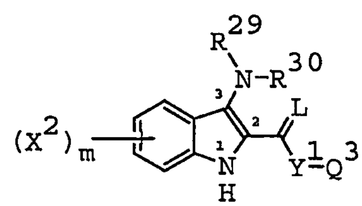
[0155] The COX-2 inhibitors that may be used in the present invention do not include the 2,3-substituted indole compounds described in WO 99/35130 as compounds of formula (1) or the pharmaceutically acceptable salts thereof



(1)

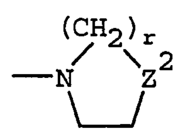
[0156] wherein Z^1 is OH, C_{1-6} alkoxy, $-NR^{27}R^{28}$ or heterocycle; Q is selected from the following: (a) an optionally substituted phenyl, (b) an optionally substituted 6-membered monocyclic aromatic group containing one, two, three or four nitrogen atom(s), (c) an optionally substituted 5-membered monocyclic aromatic group containing one heteroatom selected from O, S and N and optionally containing one, two or three nitrogen atom(s) in addition to said heteroatom, (d) an optionally substituted C_{3-7} cycloalkyl and (e) an optionally substituted benzofused heterocycle; R^{26} is hydrogen, C_{1-4} alkyl or halo; R^{27} and R^{28} are independently hydrogen, OH, C_{1-4} alkoxy, C_{1-4} alkyl or C_{1-4} alkyl substituted with halo, OH, C_{1-4} alkoxy or CN; X^1 is independently selected from H, halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, OH, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, NO_2, NH_2, di-(C_{1-4} alkyl)amino and CN; and t is 0, 1, 2, 3 and 4.

[0157] The COX-2 inhibitors that may be used in the present invention also do not include the 2,3-substituted indole compounds described in U.S. Patent No. 6,277,878 as compounds of formula (2) or the pharmaceutically acceptable salts thereof



(2)

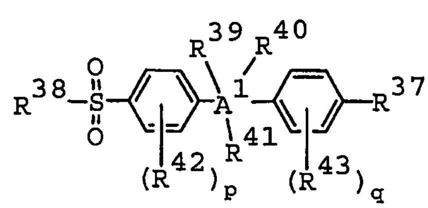
wherein R^{29} is H or C_{1-4} alkyl; R^{30} is $C(=L^1)R^{31}$ or SO_2R^{32}; Y^1 is a direct bond or C_{1-4} alkylene; L and L^1 are independently oxygen or sulfur; Q^3 is selected from the following: C_{1-6} alkyl, halo-substituted C_{1-4} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted phenyl or naphthyl, optionally substituted 5 or 6-membered monocyclic aromatic group; R^{31} is $-OR^{34}$, $-NR^{35}R^{36}$, $N(OR^{29})R^{35}$ or a group of formula;



Z^2 is a direct bond, O, S or NR^{33}; R^{32} is C_{1-6} alkyl, halo-substituted C_{1-4} alkyl, optionally substituted phenyl or naphthyl; R^{33} is C_{1-4} alkyl or halo-substituted C_{1-4} alkyl; R^{34} is C_{1-4} alkyl C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, halo-substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkyl-phenyl or phenyl; R^{35} and R^{36} are each

selected from the following: H, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{1-4} alkyl-C_{3-7} cycloalkyl, and optionally substituted C_{1-4} alkyl-phenyl or phenyl; X^2 is each selected from halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, OH, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, NO_2, NH_2, di-(C_{1-4} alkyl)amino and CN; m is 0, 1, 2 or 3; and r is 1, 2 or 3.

[0158] Further, the COX-2 inhibitors that may be used in the present invention do not include the tetracyclic sulfonylbenzene compounds described in U.S. Patent No. 6,294,558 as compounds of formula (3) or the pharmaceutically acceptable salts thereof



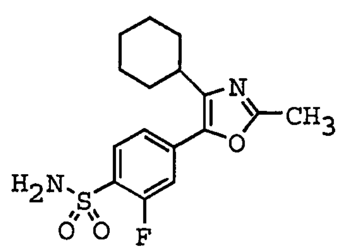
(3)

wherein A^1 is partially unsaturated or unsaturated five membered heterocyclic, or partially unsaturated or unsaturated five membered carbocyclic, wherein the 4-(sulfonyl)phenyl and the 4-substituted phenyl in the formula (3) are attached to ring atoms of Ring A^1, which are adjacent to each other; R^{37} is optionally substituted aryl or heteroaryl, with the proviso that when A^1 is pyrazole, R^{37} is heteroaryl; R^{38} is C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{1-4} alkylamino, C_{1-4} dialkylamino or amino; R^{39}, R^{40} and R^{41} are independently hydrogen, halo, C_{1-4} alkyl, halo-substituted C_{1-}

$_4$ alkyl or the like; or two of R^{39}, R^{40} and R^{41} are taken together with atoms to which they are attached and form a 4-7 membered ring; R^{42} and R^{43} are independently hydrogen, halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino or N,N-di-C_{1-4} alkylamino; and p and q are independently 1, 2, 3 or 4.

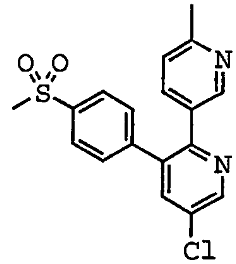
[0159] Cyclooxygenase-2 selective inhibitors that are useful in the present invention can be supplied by any source as long as the cyclooxygenase-2-selective inhibitor is pharmaceutically acceptable. Cyclooxygenase-2-selective inhibitors can be isolated and purified from natural sources or can be synthesized. Cyclooxygenase-2-selective inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[0160] Further preferred COX-2 inhibitors that may be used in the present invention include, but are not limited to:



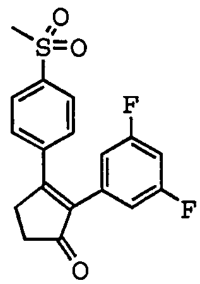
(C1)

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide;



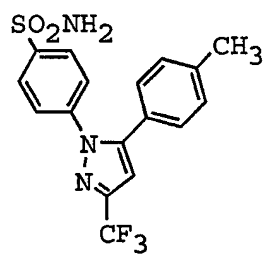
(C2)

MK-663, etoricoxib, 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine;



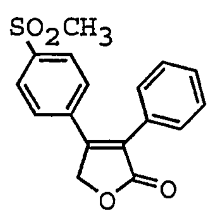
(C3)

L-776,967, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;



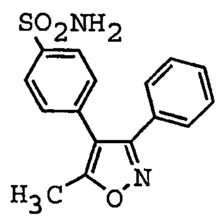
(C4)

celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;



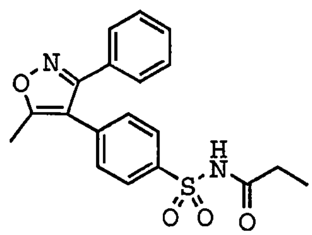
(C5)

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone;



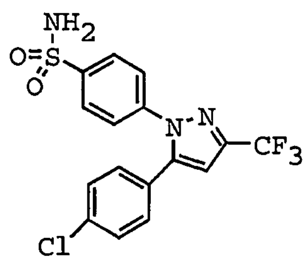
(C6)

valdecoxib, 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;



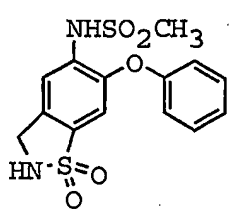
(C7)

parecoxib, N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;



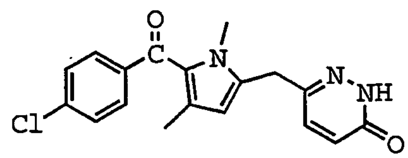
(C8)

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;



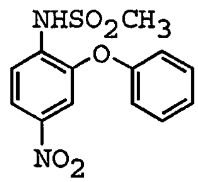
(C9)

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide;



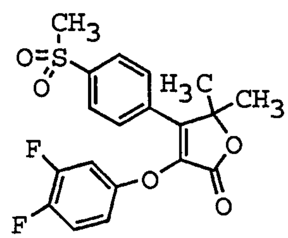
(C10)

6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;



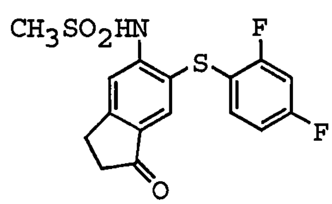
(C11)

nimesulide, N-(4-nitro-2-phenoxyphenyl)methanesulfonamide;



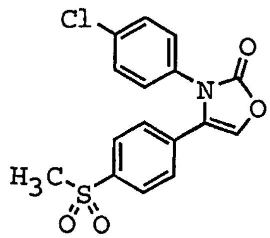
(C12)

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;



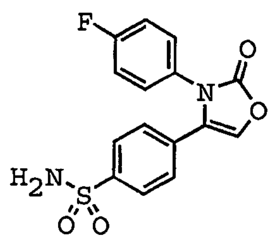
(C13)

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;



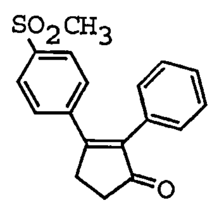
(C14)

3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;



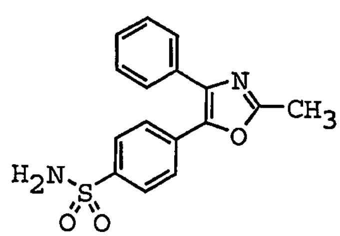
(C15)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;



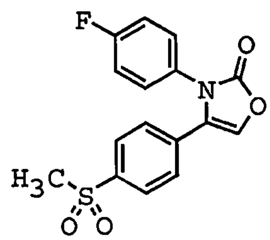
(C16)

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one;



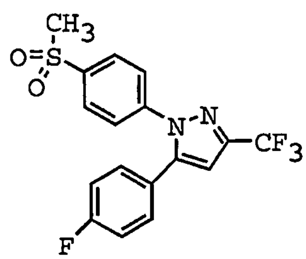
(C17)

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide;



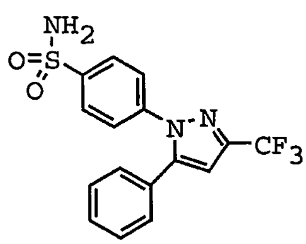
(C18)

3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;



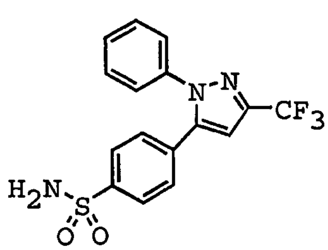
(C19)

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;



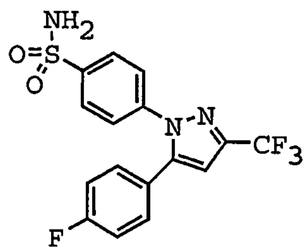
(C20)

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;



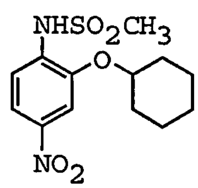
(C21)

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;



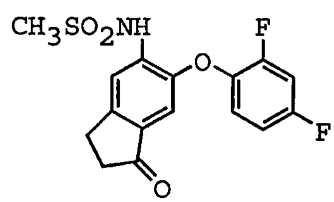
(C22)

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;



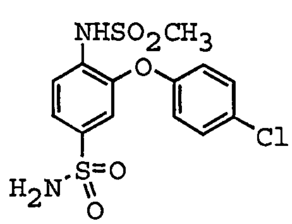
(C23)

NS-398, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide;



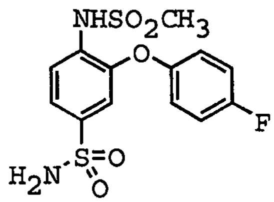
(C24)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;



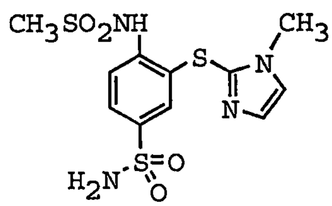
(C25)

3-(4-chlorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide;



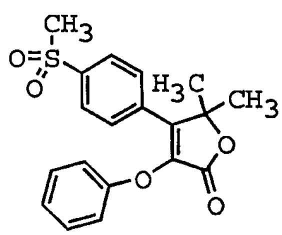
(C26)

3-(4-fluorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide;



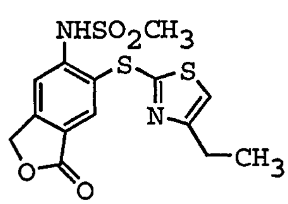
(C27)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4 [(methylsulfonyl) amino]benzenesulfonamide;



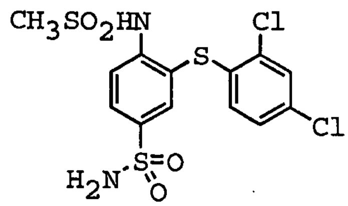
(C28)

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-phenoxy-2(5H)-furanone;



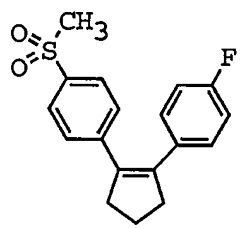
(C29)

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide;



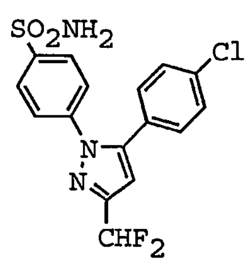
(C30)

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide;



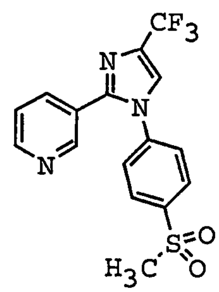
(C31)

1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene;



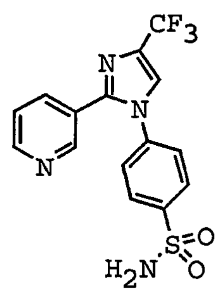
(C32)

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;



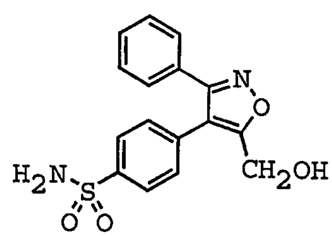
(C33)

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;



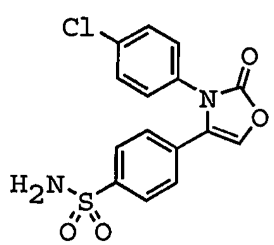
(C34)

4-[2-(3-pyridinyl1)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;



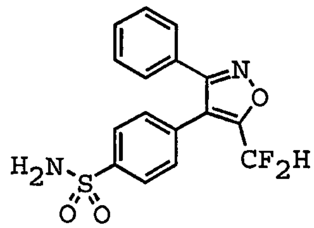
(C35)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;



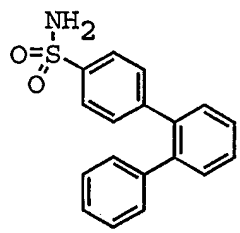
(C36)

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;



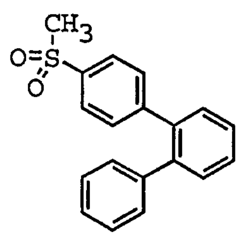
(C37)

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;



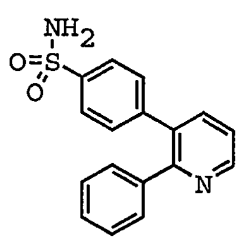
(C38)

[1,1′:2′,1″-terphenyl]-4-sulfonamide;



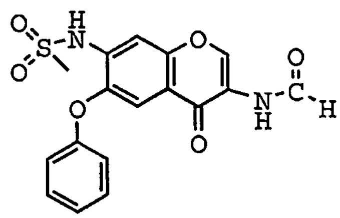
(C39)

4-(methylsulfonyl)-1,1′,2],1″-terphenyl;



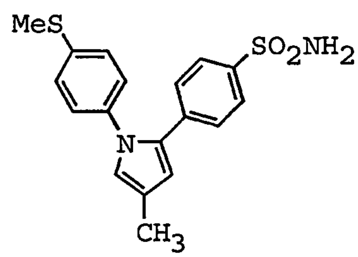
(C40)

4-(2-phenyl-3-pyridinyl)benzenesulfonamide;



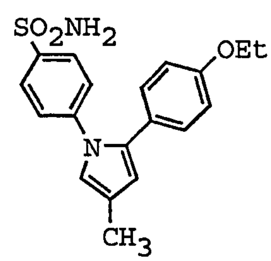
(C41)

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide;



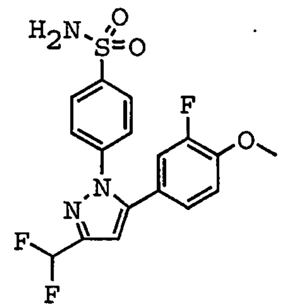
(C42)

4-[4-methyl-1-[4-(methylthio)phenyl]-1H-pyrrol-2-yl]benzenesulfonamide;



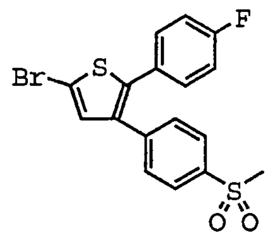
(C43)

4-[2-(4-ethoxyphenyl)-4-methyl-1H-pyrrol-1-yl]benzenesulfonamide;



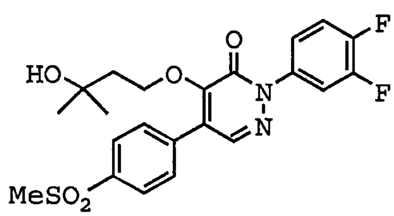
(C44)

deracoxib, 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;



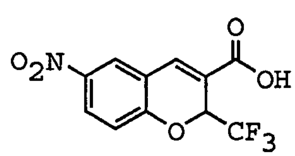
(C45)

DuP 697, 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene;



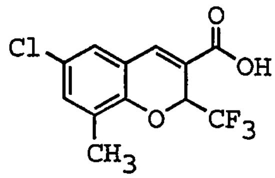
(C46)

ABT-963, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;



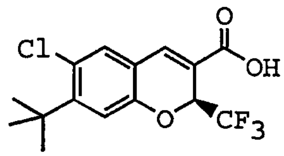
(C47)

6-nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;



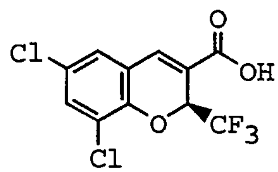
(C48)

6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;



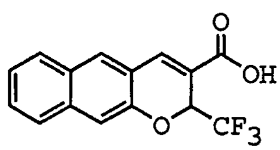
(C49)

(2S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



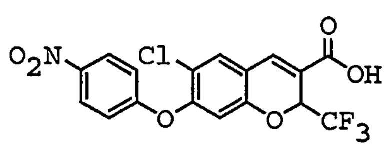
(C50)

SD-8381, (2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



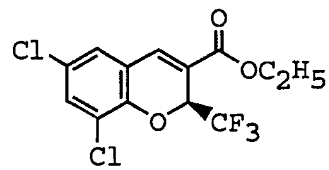
(C51)

2-trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid;



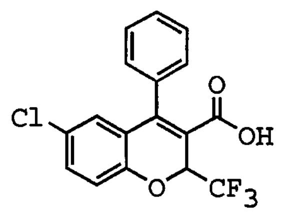
(C52)

6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



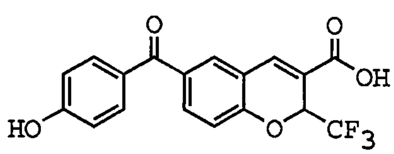
(C53)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, ethyl ester;



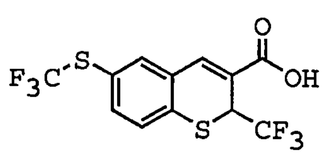
(C54)

6-chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid;



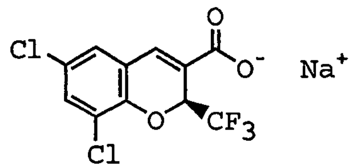
(C55)

6-(4-hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



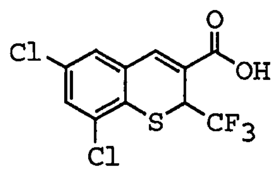
(C56)

2-(trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid;



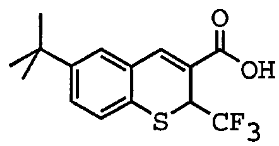
(C57)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, sodium salt;



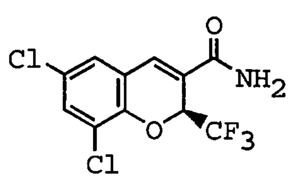
(C58)

6,8-dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;



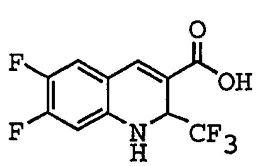
(C59)

6-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid;



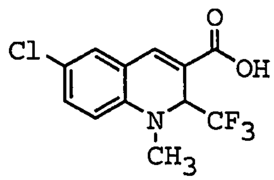
(C60)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxamide;



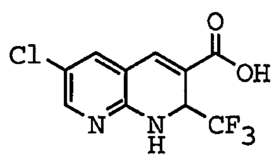
(C61)

6,7-difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid;



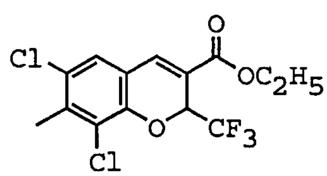
(C62)

6-chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid;



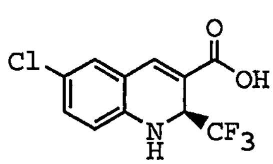
(C63)

6-chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid;



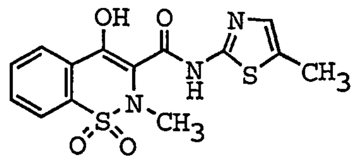
(C64)

6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, ethyl ester;



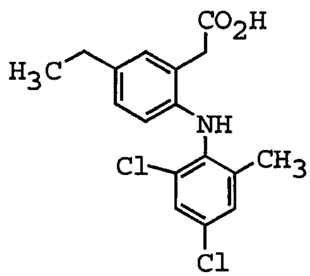
(C65)

(2S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid;



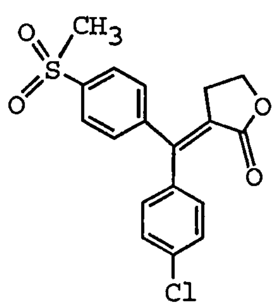
(C66)

meloxicam, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide, 1,1-dioxide;



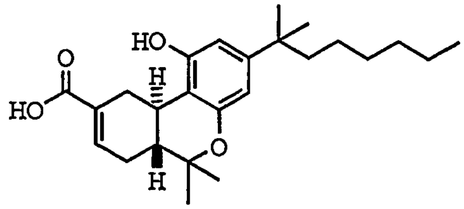
(C67)

COX-189, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid;



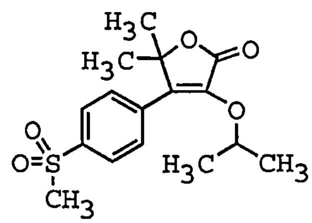
(C68)

BMS 347070, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone;



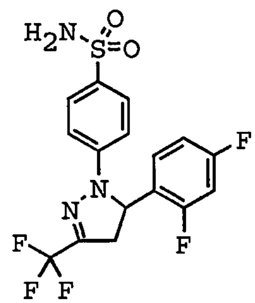
(C69)

CT3, ajulemic acid, (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid;



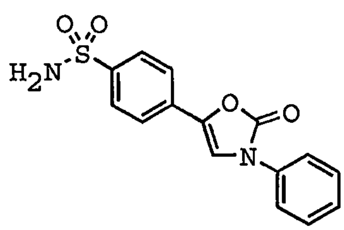
(C70)

DFP, 5,5-dimethyl-3-(1-methylethoxy)-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;



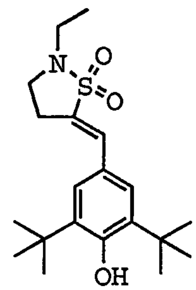
(C71)

E-6087, 4-[5-(2,4-difluorophenyl)-4,5-dihydro-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;



(C72)

LAS-33815, 3-phenyl-4-(4-aminosulfonylphenyl)oxazol-2(3H)-one; and



(C73)

S-2474, 2,6-bis(1,1-dimethylethyl)-4-[(E)-(2-ethyl-1,1-dioxido-5-isothiazolidinylidene)methyl]-phenol.

[0161] The CAS reference numbers for nonlimiting examples of COX-2 inhibitors are identified in Table No. 3 below.

[0162] Table No. 3. COX-2 Inhibitor's CAS Reference Numbers

Compound Number	CAS Reference Number
C1	180200-68-4
C2	202409-33-4
C3	212126-32-4
C4	169590-42-5
C5	162011-90-7
C6	181695-72-7
C7	198470-84-7
C8	170569-86-5
C9	187845-71-2
C10	179382-91-3
C11	51803-78-2
C12	189954-13-0
C13	158205-05-1
C14	197239-99-9
C15	197240-09-8
C16	226703-01-1
C17	93014-16-5
C18	197239-97-7

Compound Number	CAS Reference Number
C19	162054-19-5
C20	170569-87-6
C21	279221-13-5
C22	170572-13-1
C23	123653-11-2
C24	80937-31-1
C25	279221-14-6
C26	279221-15-7
C27	187846-16-8
C28	189954-16-3
C29	181485-41-6
C30	187845-80-3
C31	158959-32-1
C32	170570-29-3
C33	177660-77-4
C34	177660-95-6
C35	181695-81-8
C36	197240-14-5
C37	181696-33-3
C38	178816-94-9
C39	178816-61-0
C40	279221-17-9
C41	123663-49-0
C42	197905-01-4
C43	197904-84-0
C44	169590-41-4
C45	88149-94-4
C46	266320-83-6
C47	215122-43-3
C48	215122-44-4
C49	215122-74-0

Compound Number	CAS Reference Number
C50	215123-80-1
C51	215122-70-6
C52	264878-87-7
C53	279221-12-4
C54	215123-48-1
C55	215123-03-8
C56	215123-60-7
C57	279221-18-0
C58	215123-61-8
C59	215123-52-7
C60	279221-19-1
C61	215123-64-1
C62	215123-70-9
C63	215123-79-8
C64	215123-91-4
C65	215123-77-6
C66	71125-38-7
C67	220991-33-3
C68	197438-41-8
C69	137945-48-3
C70	189954-66-3
C71	251442-94-1
C73	158089-95-3

[0163] Nonlimiting examples of COX-2 inhibitors that may be used in the present invention are identified in Table No. 4 below. The individual references in Table No. 4 are each herein individually incorporated by reference.

[0164] Table No. 4. COX-2 Inhibitors

Compound	Trade/Research Name	Reference	Dosage
6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide, 1,1-dioxide	lornoxicam; Safem®	CAS No. 70374-39-9	
1,5-Diphenyl-3-substituted pyrazoles		WO 97/13755	
	radicicol	WO 96/25928. Kwon et al (Cancer Res(1992) 52 6296)	
	GB-02283745		
	TP-72	Cancer Res 1998 58 4 717 -723	
1-(4-chlorobenzoyl)-3-[4-(4-fluoro-phenyl)thiazol-2-ylmethyl]-5-methoxy-2-methylindole	A-183827.0		
	GR-253035		
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	JTE-522	JP 9052882	
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)-pyridine			
2-(3,5-difluoro-phenyl)-3-4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one			
	L-768277		
	L-783003		
	MK-966; VIOXX®, Rofecoxib	US 5968974	12.5-100 mg po

Compound	Trade/Research Name	Reference	Dosage
indomethacin-derived indolalkanoic acid		WO 96/374679	200 mg/kg/day
1-Methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene		WO 95/30656. WO 95/30652. WO 96/38418. WO 96/38442.	
4,4-dimethyl-2-phenyl-3-[4-(methylsulfonyl)phenyl]cyclo-butenone			
2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole		EP 799823	
N-[5-(4-fluoro)phenoxy]thiophene-2-methanesulfon-amide	RWJ-63556		
5(E)-(3,5-di-tert-butyl-4-hydroxy)benzylidene-2-ethyl-1,2-isothiazolidine-1,1-dioxide	S-2474	EP 595546	
3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one	T-614	DE 3834204	
Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-	celecoxib	US 5466823	
CS 502	(Sankyo)		
MK 633	(Merck)		
	meloxicam	US 4233299	15-30 mg/day
	nimesulide	US 3840597	

[0165] The following references listed in Table No. 5 below, hereby individually incorporated by reference, describe

various COX-2 inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

[0166] Table No. 5. COX-2 Inhibitor References

WO 99/30721	WO 99/30729	US 5760068	WO 98/15528
WO 99/25695	WO 99/24404	WO 99/23087	FR 27/71005
EP 921119	FR 27/70131	WO 99/18960	WO 99/15505
WO 99/15503	WO 99/14205	WO 99/14195	WO 99/14194
WO 99/13799	GB 23/30833	US 5859036	WO 99/12930
WO 99/11605	WO 99/10332	WO 99/10331	WO 99/09988
US 5869524	WO 99/05104	US 5859257	WO 98/47890
WO 98/47871	US 5830911	US 5824699	WO 98/45294
WO 98/43966	WO 98/41511	WO 98/41864	WO 98/41516
WO 98/37235	EP 86/3134	JP 10/175861	US 5776967
WO 98/29382	WO 98/25896	ZA 97/04806	EP 84/6,689
WO 98/21195	GB 23/19772	WO 98/11080	WO 98/06715
WO 98/06708	WO 98/07425	WO 98/04527	WO 98/03484
FR 27/51966	WO 97/38986	WO 97/46524	WO 97/44027
WO 97/34882	US 5681842	WO 97/37984	US 5686460
WO 97/36863	WO 97/40012	WO 97/36497	WO 97/29776
WO 97/29775	WO 97/29774	WO 97/28121	WO 97/28120
WO 97/27181	WO 95/11883	WO 97/14691	WO 97/13755
WO 97/13755	CA 21/80624	WO 97/11701	WO 96/41645
WO 96/41626	WO 96/41625	WO 96/38418	WO 96/37467
WO 96/37469	WO 96/36623	WO 96/36617	WO 96/31509
WO 96/25405	WO 96/24584	WO 96/23786	WO 96/19469
WO 96/16934	WO 96/13483	WO 96/03385	US 5510368
WO 96/09304	WO 96/06840	WO 96/06840	WO 96/03387
WO 95/21817	GB 22/83745	WO 94/27980	WO 94/26731
WO 94/20480	WO 94/13635	FR 27/70,131	US 5859036
WO 99/01131	WO 99/01455	WO 99/01452	WO 99/01130
WO 98/57966	WO 98/53814	WO 98/53818	WO 98/53817

WO 98/47890	US 5830911	US 5776967	WO 98/22101
DE 19/753463	WO 98/21195	WO 98/16227	US 5733909
WO 98/05639	WO 97/44028	WO 97/44027	WO 97/40012
WO 97/38986	US 5677318	WO 97/34882	WO 97/16435
WO 97/03678	WO 97/03667	WO 96/36623	WO 96/31509
WO 96/25928	WO 96/06840	WO 96/21667	WO 96/19469
US 5510368	WO 96/09304	GB 22/83745	WO 96/03392
WO 94/25431	WO 94/20480	WO 94/13635	JP 09052882
GB 22/94879	WO 95/15316	WO 95/15315	WO 96/03388
WO 96/24585	US 5344991	WO 95/00501	US 5968974
US 5945539	US 5994381	US 5521207	

<u>TOPOISOMERASE II INHIBITORS</u>

[0167] Topoisomerase II inhibitors are useful in the prevention and treatment of neoplasia disorders.

[0168] Some topoisomerase II inhibitors are members of the antibiotic-type antineoplastic agent family. Suitable antibiotic-type antineoplastic agents that may be used in the present invention include, but are not limited to aclarubicin, Bristol-Myers BMY-27557, daunorubicin, ditrisarubicin B, doxorubicin, doxorubicin-fibrinogen, epirubicin, esorubicin, fostriecin, idarubicin, menogaril, mitoxantrone, pirarubicin, rodorubicin, and zorubicin.

[0169] Some antibiotic anticancer agents that may be used in the present invention include, but are not limited to, those agents identified in Table No. 6, below.

[0170] <u>Table No. 6.</u> Antibiotic anticancer agents

Compound	Common Name/ Trade Name	Company	Reference	Dosage
	mitoxan-trone		US 4310666	
	doxorubicin		US 3590028	

[0171] Some topoisomerase II inhibitors are members of a miscellaneous antineoplastic agent family. Suitable topoisomerase II inhibitors that are members of a miscellaneous family of antineoplastic agents that may be used in the present invention include, but are not limited to amonafide, amsacrine, crisnatol, etoposide, merbarone, and teniposide.

[0172] Preferred topoisomerase II inhibitors that may be used in the present invention include, but are not limited to, the group consisting of

amrubicin;

amsacrine;

annamycin;

6,9-bis[(2-aminoethyl)amino]-benz[g]isoquinoline-5,10-dione;

1,11-dichloro-6-[2-(diethylamino)ethyl]-12,13-dihydro-12-(4-O-methyl-β-D-glucopyranosyl)-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

daunorubicin;

doxorubicin;

epirubicin;

etoposide;

galarubicin;

(5R,5aR,8aS,9S)- 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[(4-nitrophenyl)amino]-furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one;

idarubicin;

iododoxorubicin;

10-[[6-deoxy-2-O-(6-deoxy-3-O-methyl-α-D-galactopyranosyl)-3,4-O-[(S)-phenylmethylene]-β-D-galactopyranosyl]oxy]-5,12-dihydro-1-methyl-5,12-dioxobenzo[h][1]benzopyrano[5,4,3-cde][1]benzopyran-6-yl ester-3-ethoxy-propanoic acid;

8-ethyl-7,8,9,10-tetrahydro-1,6,7,8,11-pentahydroxy-10-[[2,3,6-trideoxy-3-(4-morpholinyl)-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione;

(7S,9S)-7-[[4-O-(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)-2,6-dideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxyacetyl)-5,12-naphthacenedione;

merbarone;

mitoxantrone;

nemorubicin;

(5R,5aR,8aS,9S)- 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[(4-nitrophenyl)amino]-furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one;

pirarubicin;

N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide;

sobuzoxane;

teniposide; and

valrubicin;

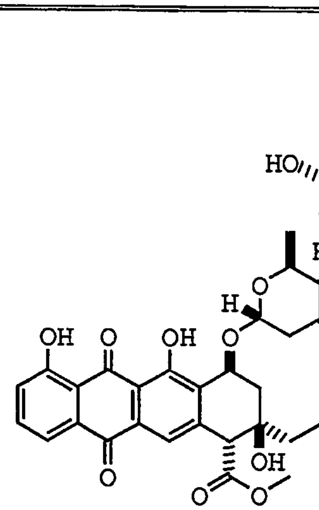
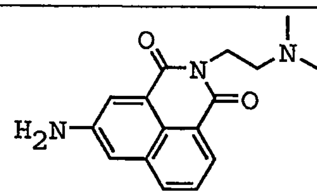
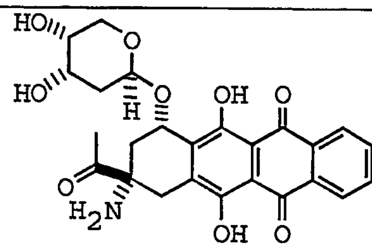
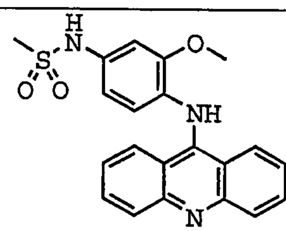
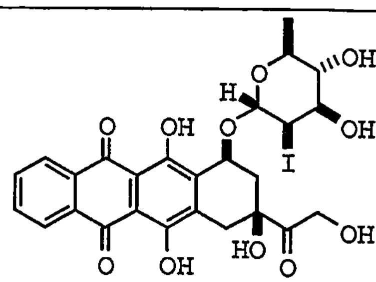
or a pharmaceutically acceptable salt thereof.

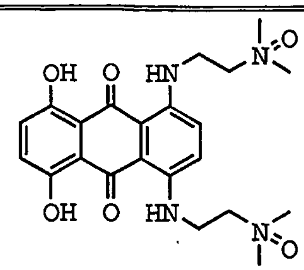
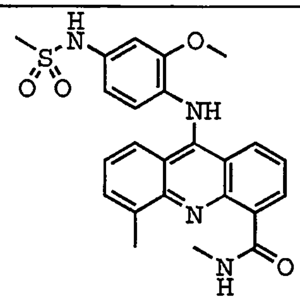
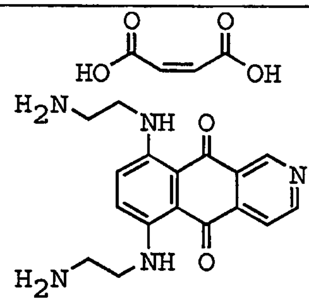
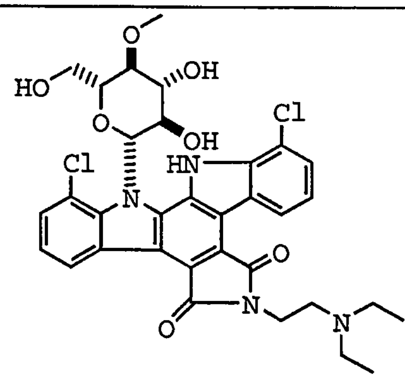
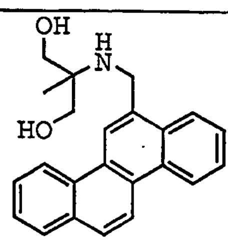
More preferably, the topoisomerase II inhibitor is selected from the group consisting of amrubicin, amsacrine, daunorubicin, doxorubicin, epirubicin, etoposide, idarubicin, mitoxantrone, nemorubicin, pirarubicin, sobuzoxane, teniposide, and valrubicin, or a pharmaceutically acceptable salt thereof.

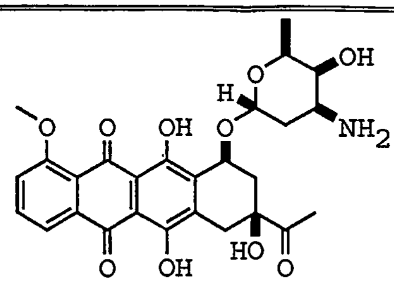
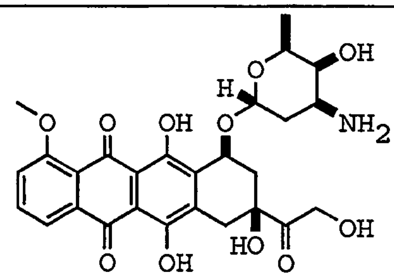
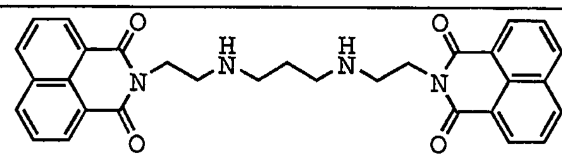
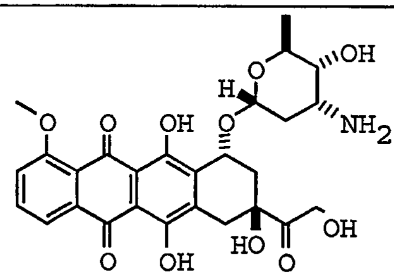
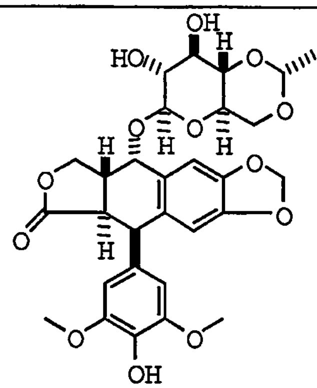
[0173] Most preferably, the topoisomerase II inhibitor is epirubicin or idarubicin, or a pharmaceutically acceptable salt thereof.

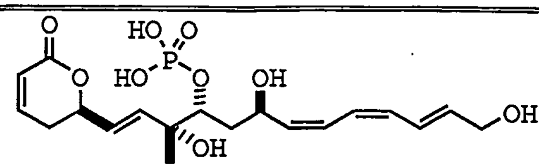
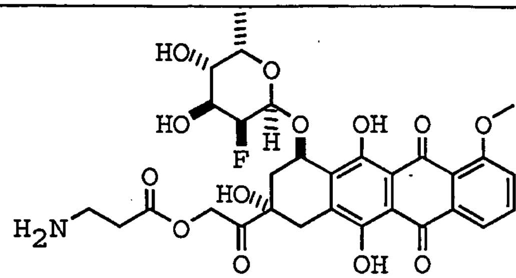
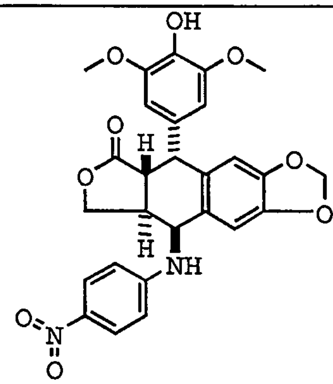
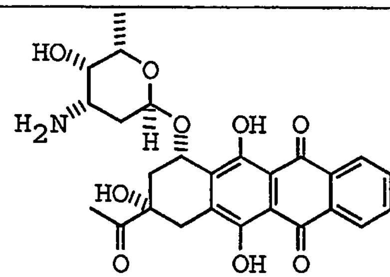
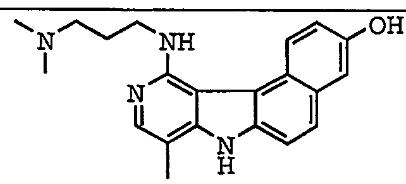
[0174] The structures of preferred topoisomerase II inhibitors are listed in Table No. 7 below.

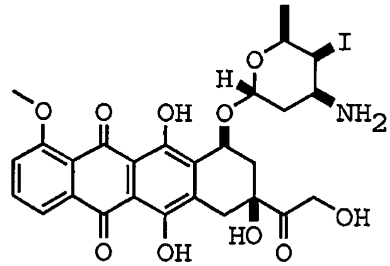
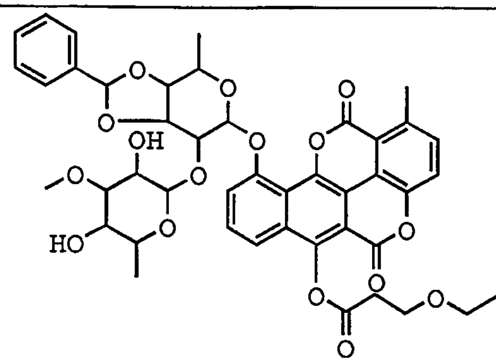
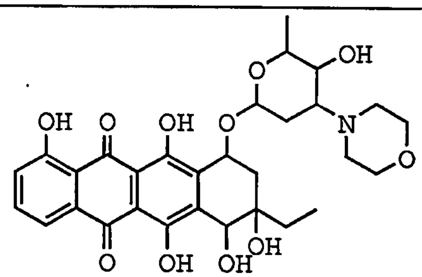
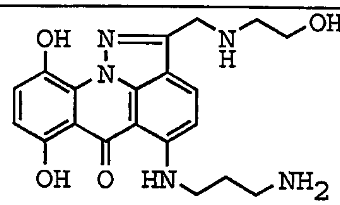
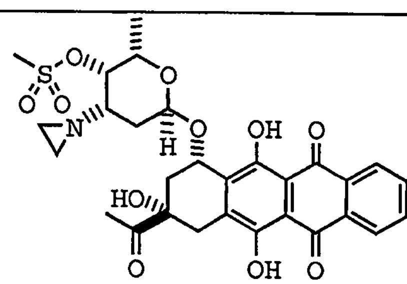
[0175] Table No. 7. Topoisomerase II Inhibitors

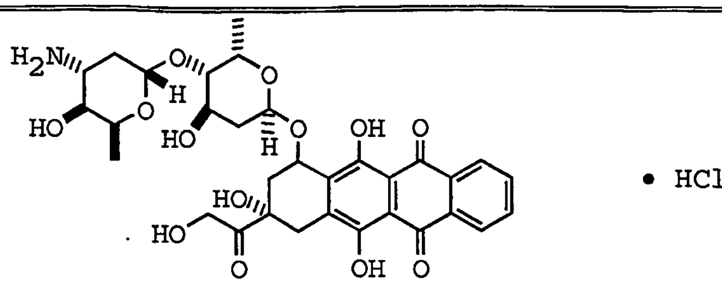
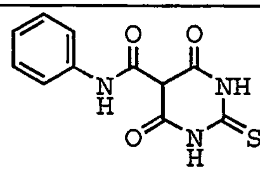
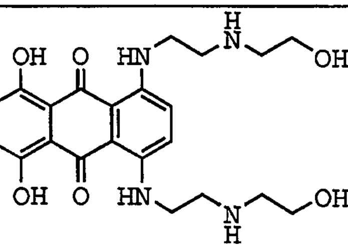
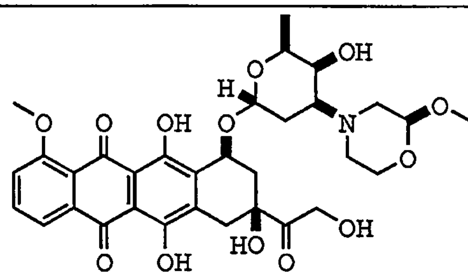
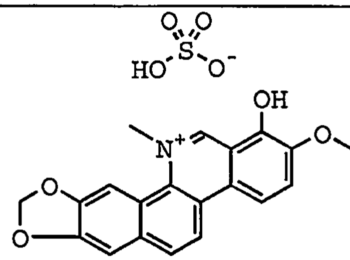
Compound Number	Structure
T1	
T2	
T3	
T4	
T5	

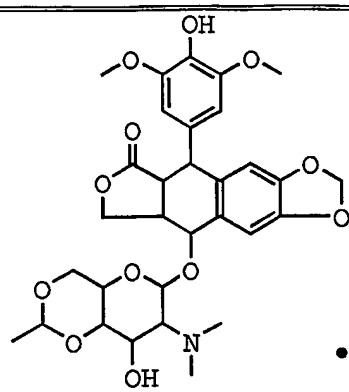
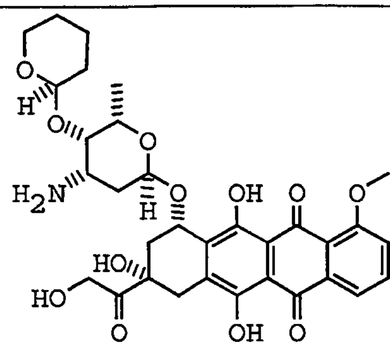
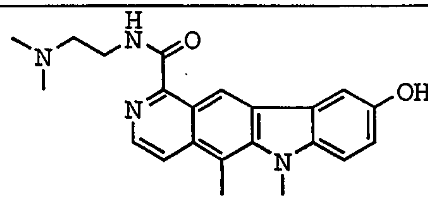
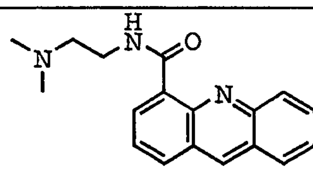
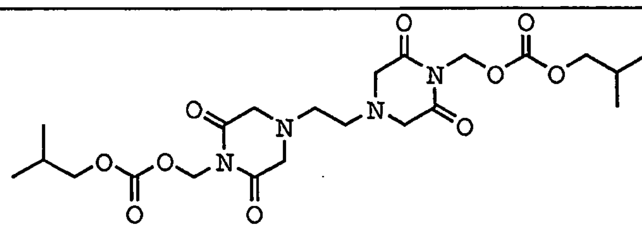
Compound Number	Structure
T6	
T7	
T8	
T9	
T10	

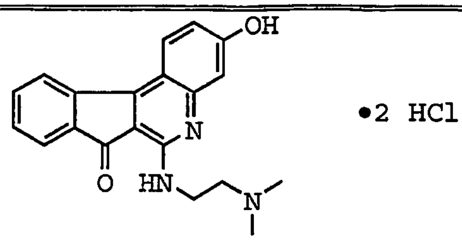
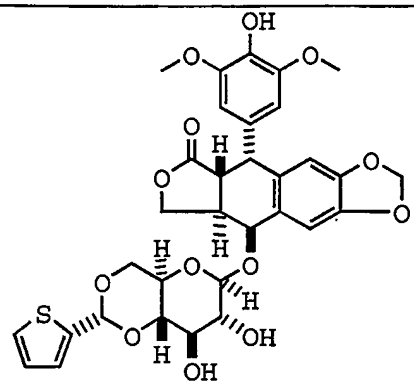
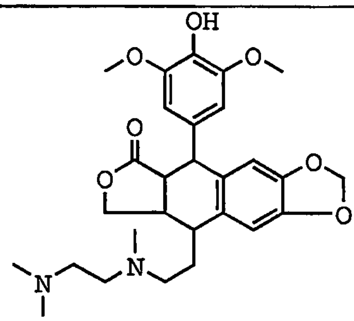
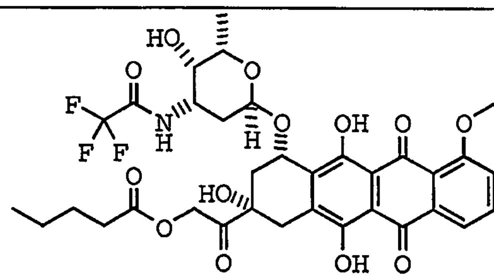
Compound Number	Structure
T11	
T12	
T13	
T14	 •HCl
T15	

Compound Number	Structure
T16	
T17	 • HCl
T18	
T19	
T20	

Compound Number	Structure
T21	
T22	
T23	
T24	 •2 HCl
T25	

Compound Number	Structure
T26	
T27	
T28	
T29	
T30	

Compound Number	Structure
T31	 • HCl
T32	
T33	 •2 HCl
T34	 •2 HCl
T35	

Compound Number	Structure
T36	
T37	
T38	
T39	

[0176] The names, CAS registry numbers and references for preferred topoisomerase II inhibitors are listed in Table No. 8 below. The individual references in Table No. 8 are each herein individually incorporated by reference.

[0177] Table No. 8. Topoisomerase II Inhibitor Names, CAS Registry Numbers and References

Compound Number	Name(s)	CAS Registry Number	Reference
T1	Aclarubicin	57576-44-0	US 4375511
T2	Amonafide	69408-81-7	US 4204063
T3	Amrubicin	110267-81-7	US 4673668
T4	Amsacrine	51264-14-3	US 4258191
T5	Annamycin	92689-49-1	US 4537882
T6	AQ4N, 1,4-bis[[2-(dimethyl-oxidoamino)ethyl]amino]-5,8-dihydroxy-9,10-anthracenedione	136470-65-0	US 5132327
T7	Asulacrine	80841-47-0	US 4366318
T8	BBR-2778, 6,9-bis[(2-aminoethyl)amino]-benz[g]isoquinoline-5,10-dione, (2Z)-2-butenedioate (1:2)	144675-97-8	WO 9215300
T9	BMY-27557, 1,11-dichloro-6-[2-(diethylamino)ethyl]-12,13-dihydro-12-(4-O-methyl-β-D-glucopyranosyl)-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione	119673-08-4	US 4785085
T10	Crisnatol	96389-68-3	US 4530800
T11	Daunorubicin	20830-81-3	BR 1003383
T12	Doxorubicin	23214-92-8	US 3590028
T13	Elinafide	162706-37-8	WO 9505365
T14	epirubicin hydrochloride	56390-09-1	US 4058519
T15	Etoposide	33419-42-0	CH 514578

Compound Number	Name(s)	CAS Registry Number	Reference
T16	Fostriecin	87810-56-8	US 4578383
T17	galarubicin hydrochloride	140637-82-7	US 5220001
T18	GL-331, (5R,5aR,8aS,9S)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[(4-nitrophenyl)amino]-furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one	127882-73-9	US 5300500
T19	Idarubicin	58957-92-9	US 4046878
T20	Intoplicine	125974-72-3	US 5091388
T21	Iododoxorubicin	83997-75-5	US 4438105
T22	IST-622, 10-[[6-deoxy-2-O-(6-deoxy-3-O-methyl-α-D-galactopyranosyl)-3,4-O-[(S)-phenylmethylene]-β-D-galactopyranosyl]oxy]-5,12-dihydro-1-methyl-5,12-dioxobenzo[h][1]benzopyrano[5,4,3-cde][1]benzopyran-6-yl ester-3-ethoxy-propanoic acid	128201-92-3	JP 2651707
T23	MX-2, 8-ethyl-7,8,9,10-tetrahydro-1,6,7,8,11-pentahydroxy-10-[[2,3,6-trideoxy-3-(4-morpholinyl)-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione	105026-50-4	US 4710564

Compound Number	Name(s)	CAS Registry Number	Reference
T24	KW-2170, 5-[(3-aminopropyl)amino]-7,10-dihydroxy-2-[[(2-hydroxyethyl)amino]methyl]-6H-pyrazolo[4,5,1-de]acridin-6-one, dihydrochloride	207862-44-0	US 5220026
T25	Ladirubicin	171047-47-5	US 5532218
T26	MEN-10755, (7S,9S)-7-[[4-O-(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)-2,6-dideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-9-(hydroxyacetyl)-5,12-naphthacenedione, hydrochloride	169317-77-5	US 5801152
T27	Merbarone	97534-21-9	US 4634707
T28	Mitoxantrone	65271-80-9	US 4197249
T29	Nemorubicin	108852-90-0	US 4672057
T30	NK-109, 1-hydroxy-2-methoxy-12-methyl-[1,3]benzodioxolo[5,6-c]phenanthridinium, sulfate (1:1) (salt)	143201-31-4	EP 487930

Compound Number	Name(s)	CAS Registry Number	Reference
T31	NK-611, (5R,5aR,8aR,9S)-9-[[2-deoxy-2-(dimethylamino)-4,6-O-(1R)-ethylidene-β-D-glucopyranosyl]oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one, hydrochloride	105760-98-3	US 4716221
T32	Pirarubicin	72496-41-4	EP 14853
T33	S-16020-2, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, dihydrochloride	178169-99-8	EP 591058
T34	SN-22995, N-[2-(dimethylamino)ethyl]-4-acridinecarboxamide, dihydrochloride	89458-99-1	US 4590277
T35	Sobuzoxane	98631-95-9	US 4650799
T36	TAS-103, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, dihydrochloride	174634-09-4	WO 9532187
T37	Teniposide	29767-20-2	US 3524844

Compound Number	Name(s)	CAS Registry Number	Reference
T38	TOP-53, (5R,5aR,8aR,9S)-9-[2-[[2-(dimethylamino)-ethyl]methylamino]ethyl]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-furo[3',4':6,7]naphtho[2,3-d]-1,3-dioxol-6(5aH)-one	148262-19-5	WO 9212982
T39	Valrubicin	56124-62-0	US 4035566

[0178] Various formulations and delivery systems have been developed for topoisomerase II inhibitors including the following for doxorubicin: MTC-DOX (magnetic targeted carrier delivery system, FeRX Inc.), LED (liposome encapsulated, NeoPharm Inc.), Doxil (pegylated STEALTH liposomal formulation, ALZA Corp.), Myocet (liposomal formulation, The Liposome Company Inc.), SGN-15 (monoclonal antibody-doxorubicin conjugate, Seattle Genetics Inc.), SP-1049C (formulation with a Biotransport carrier, Supratek Pharma, Inc.), PK1 (doxorubicin attached to a sugar molecule and N-(2-hydroxypropyl)methyacrylamide (HMPA) copolymer by a peptidyl linker, Pharmacia & Upjohn Inc., CAS No. 171714-74-2), and PK2 (N-(2-hydroxypropyl)methyacrylamide (HMPA) copolymer-galactose-doxorubicin conjugate, Pharmacia & Upjohn Inc., CAS No. 187620-05-9). DaunoXome is a liposomal formulation of daunorubicin citrate developed by NeXstar Pharmaceuticals Inc. The preceding formulations, among others, may be used with the compositions and therapies of the present invention.

[0179] The doxorubicin used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 3,590,028. The etoposide

used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,564,675. The mitoxantrone used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,310,666.

[0180] The compounds useful in the present invention can have no asymmetric carbon atoms, or, alternatively, the useful compounds can have one or more asymmetric carbon atoms. When the useful compounds have one or more asymmetric carbon atoms, they therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

[0181] Isomers may include geometric isomers, for example cis-isomers or trans-isomers across a double bond. All such isomers are contemplated among the compounds useful in the present invention.

[0182] Also included in the methods, combinations and compositions of the present invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

[0183] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic

ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

[0184] Also included in the methods, combinations and compositions of the present invention are the prodrugs of the described compounds and the pharmaceutically-acceptable salts thereof. The term "prodrug" refers to drug precursor compounds which, following administration to a subject and subsequent absorption, are converted to an active species in vivo via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. More preferred prodrugs produce products from the conversion process that are generally accepted as safe. A nonlimiting example of a "prodrug" that will be useful in the methods, combinations and compositions of the present invention is parecoxib, (N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl]propanamide). Another illustrative example of a "prodrug" is etoposide phosphate (CAS No. 117091-64-2) which may be prepared as described in U.S. Patent No. 4,904,768.

[0185] The methods and combinations of the present invention are useful for the treatment, prevention or inhibition of neoplasia or a neoplasia-related disorder

including malignant tumor growth, benign tumor growth and metastasis.

[0186] Malignant tumor growth locations comprise the nervous system, cardiovascular system, circulatory system, respiratory tract, lymphatic system, hepatic system, musculoskeletal system, digestive tract, renal system, male reproductive system, female reproductive system, urinary tract, nasal system, gastrointestinal tract, dermis, and head and neck region.

[0187] Malignant tumor growth locations in the nervous system comprise the brain and spine.

[0188] Malignant tumor growth locations in the respiratory tract system comprise the lung and bronchus.

[0189] Malignant tumor growths in the lymphatic system comprise Hodgkin's lymphoma and non-Hodgkin's lymphoma.

[0190] Malignant tumor growth locations in the hepatic system comprise the liver and intrahepatic bile duct.

[0191] Malignant tumor growth locations in the musculoskeletal system comprise bone, bone marrow, joint, muscle and connective tissue.

[0192] Malignant tumor growth locations in the digestive tract comprise the colon, small intestine, large intestine, stomach, colorectal, pancreas, liver, and rectum.

[0193] Malignant tumor growth locations in the renal system comprise the kidney and renal pelvis.

[0194] Malignant tumor growth locations in the male reproductive system comprise the prostate, penis and testicle.

[0195] Malignant tumor growth locations in the female reproductive system comprise the ovary and cervix.

[0196] Malignant tumor growth locations in the urinary tract comprise the bladder, urethra, and ureter.

[0197] Malignant tumor growth locations in the nasal sytem comprise the nasal tract and sinuses.

[0198] Malignant tumor growth locations in the gastrointestinal tract comprise the esophagus, gastric fundus, gastric antrum, duodenum, hepatobiliary, ileum, jejunum, colon, and rectum.

[0199] Malignant tumor growth in the dermis comprises melanoma and basal cell carcinoma.

[0200] Malignant tumor growth locations in the head and neck region comprise the mouth, pharynx, larynx, thyroid, and pituitary.

[0201] Malignant tumor growth locations further comprise smooth muscle, striated muscle, and connective tissue.

[0202] Malignant tumor growth locations even further comprise endothelial cells and epithelial cells.

[0203] Malignant tumor growth may be breast cancer.

[0204] Malignant tumor growth may be in soft tissue.

[0205] Malignant tumor growth may be a viral-related cancer, including cervical, T cell leukemia, lymphoma, and Kaposi's sarcoma.

[0206] Benign tumor growth locations comprise the nervous system, cardiovascular system, circulatory system, respiratory tract, lymphatic system, hepatic system, musculoskeletal system, digestive tract, renal system, male reproductive system, female reproductive system, urinary tract, nasal system, gastrointestinal tract, dermis, and head and neck region.

[0207] Benign tumor growth locations in the nervous system comprise the brain and spine.

[0208] Benign tumor growth locations in the respiratory tract system comprise the lung and bronchus.

[0209] A benign tumor growth in the lymphatic system may comprise a cyst.

[0210] Benign tumor growth locations in the hepatic system comprise the liver and intrahepatic bile duct.

[0211] Benign tumor growth locations in the musculoskeletal system comprise bone, bone marrow, joint, muscle and connective tissue.

[0212] Benign tumor growth locations in the digestive tract comprise the colon, small intestine, large intestine, stomach, colorectal, pancreas, liver, and rectum.

[0213] A benign tumor growth in the digestive tract may comprise a polyp.

[0214] Benign tumor growth locations in the renal system comprise the kidney and renal pelvis.

[0215] Benign tumor growth locations in the male reproductive system comprise the prostate, penis and testicle.

[0216] Benign tumor growth in the female reproductive system may comprise the ovary and cervix.

[0217] Benign tumor growth in the female reproductive system may comprise a fibroid tumor, endometriosis or a cyst.

[0218] Benign tumor growth in the male reproductive system may comprise benign prostatic hypertrophy (BPH) or prostatic intraepithelial neoplasia (PIN).

[0219] Benign tumor growth locations in the urinary tract comprise the bladder, urethra, and ureter.

[0220] Benign tumor growth locations in the nasal sytem comprise the nasal tract and sinuses.

[0221] Benign tumor growth locations in the gastrointestinal tract comprise the esophagus, gastric fundus, gastric antrum, duodenum, hepatobiliary, ileum, jejunum, colon, and rectum.

[0222] Benign tumor growth locations in the head and neck region comprise the mouth, pharynx, larynx, thyroid, and pituitary.

[0223] Benign tumor growth locations further comprise smooth muscle, striated muscle, and connective tissue.

[0224] Benign tumor growth locations even further comprise endothelial cells and epithelial cells.

[0225] Benign tumor growth may be located in the breast and may be a cyst or fibrocystic disease.

[0226] Benign tumor growth may be in soft tissue.

[0227] Metastasis may be from a known primary tumor site or from an unknown primary tumor site.

[0228] Metastasis may be from locations comprising the nervous system, cardiovascular system, circulatory system, respiratory tract, lymphatic system, hepatic system, musculoskeletal system, digestive tract, renal system, male reproductive system, female reproductive system, urinary tract, nasal system, gastrointestinal tract, dermis, and head and neck region.

[0229] Metastasis from the nervous system may be from the brain, spine, or spinal cord.

[0230] Metastasis from the circulatory system may be from the blood or heart.

[0231] Metastasis from the respiratory system may be from the lung or broncus.

[0232] Metastasis from the lymphatic system may be from a lymph node, lymphoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma.

[0233] Metastasis from the heptatic system may be from the liver or intrahepatic bile duct.

[0234] Metastasis from the musculoskeletal system may be from locations comprising the bone, bone marrow, joint, muscle, and connective tissue.

[0235] Metastasis from the digestive tract may be from locations comprising the colon, small intestine, large intestine, stomach, colorectal, pancreas, gallbladder, liver, and rectum.

[0236] Metastasis from the renal system may be from the kidney or renal pelvis.

[0237] Metastasis from the male reproductive system may be from the prostate, penis or testicle.

[0238] Metastasis from the female reproductive system may be from the ovary or cervix.

[0239] Metastasis from the urinary tract may be from the bladder, urethra, or ureter.

[0240] Metastasis from the gastrointestinal tract may be from locations comprising the esophagus, esophagus (Barrett's), gastric fundus, gastric antrum, duodenum, hepatobiliary, ileum, jejunum, colon, and rectum.

[0241] Metastasis from the dermis may be from a melanoma or a basal cell carcinoma.

[0242] Metastasis from the head and neck region may be from locations comprising the mouth, pharynx, larynx, thyroid, and pituitary.

[0243] Metastasis may be from locations comprising smooth muscle, striated muscle, and connective tissue.

[0244] Metastasis may be from endothelial cells or epithelial cells.

[0245] Metastasis may be from breast cancer.

[0246] Metastasis may be from soft tissue.

[0247] Metastasis may be from a viral-related cancer, including cervical, T cell leukemia, lymphoma, or Kaposi's sarcoma.

[0248] Metastasis may be from tumors comprising a carcinoid tumor, gastrinoma, sarcoma, adenoma, lipoma, myoma, blastoma, carcinoma, fibroma, or adenosarcoma.

[0249] Malignant or benign tumor growth may be in locations comprising the genital system, digestive system, breast, respiratory system, urinary system, lymphatic system, skin, circulatory system, oral cavity and pharynx, endocrine system, brain and nervous system, bones and joints, soft tissue, and eye and orbit.

[0250] Metastasis may be from locations comprising the genital system, digestive system, breast, respiratory system, urinary system, lymphatic system, skin, circulatory system,

oral cavity and pharynx, endocrine system, brain and nervous system, bones and joints, soft tissue, and eye and orbit.

[0251] The methods and compositions of the present invention may be used for the treatment, prevention or inhibition of neoplasia or neoplasia-related disorders including acral lentiginous melanoma, actinic keratoses, acute lymphocytic leukemia, acute myeloid leukemia, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, anal canal cancer, anal cancer, anorectum cancer, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, benign cysts, biliary cancer, bone cancer, bone marrow cancer, brain cancer, breast cancer, bronchial cancer, bronchial gland carcinomas, carcinoids, carcinoma, carcinosarcoma, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, chronic lymphocytic leukemia, chronic myeloid leukemia, clear cell carcinoma, colon cancer, colorectal cancer, connective tissue cancer, cystadenoma, cysts of the female reproductive system, digestive system cancer, digestive tract polyps, duodenum cancer, endocrine system cancer, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, endometriosos, endothelial cell cancer, ependymal cancer, epithelial cell cancer, esophagus cancer, Ewing's sarcoma, eye and orbit cancer, female genital cancer, fibroid tumors, focal nodular hyperplasia, gallbladder cancer, gastric antrum cancer, gastric fundus cancer, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, heart cancer, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatobiliary cancer, hepatocellular carcinoma, Hodgkin's disease, ileum cancer, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, intrahepatic bile duct cancer, invasive squamous cell carcinoma, jejunum cancer, joint cancer, Kaposi's sarcoma, kidney and renal pelvic cancer, large cell

carcinoma, large intestine cancer, larynx cancer, leiomyosarcoma, lentigo maligna melanomas, leukemia, liver cancer, lung cancer, lymphoma, male genital cancer, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal cancer, mesothelial cancer, metastatic carcinoma, mouth cancer, mucoepidermoid carcinoma, multiple myeloma, muscle cancer, nasal tract cancer, nervous system cancer, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, non-epithelial skin cancer, non-Hodgkin's lymphoma, oat cell carcinoma, oligodendroglial cancer, oral cavity cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillary serous adenocarcinoma, penile cancer, pharynx cancer, pituitary tumors, plasmacytoma, prostate cancer, pseudosarcoma, pulmonary blastoma, rectal cancer, renal cell carcinoma, respiratory system cancer, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, sinus cancer, skin cancer, small cell carcinoma, small intestine cancer, smooth muscle cancer, soft tissue cancer, somatostatin-secreting tumor, spine cancer, squamous carcinoma, squamous cell carcinoma, stomach cancer, striated muscle cancer, submesothelial cancer, superficial spreading melanoma, T cell leukemia, testis cancer, thyroid cancer, tongue cancer, undifferentiated carcinoma, ureter cancer, urethra cancer, urinary bladder cancer, urinary system cancer, uterine cervix cancer, uterine corpus cancer, uveal melanoma, vaginal cancer, verrucous carcinoma, vipoma, vulva cancer, well differentiated carcinoma, and Wilm's tumor.

[0252] The phrase "neoplasia disorder effective" or "therapeutically effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in neoplastic disease severity and the frequency of a neoplastic disease event over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

[0253] A "neoplasia disorder effect", "neoplasia disorder effective amount" or "therapeutically effective amount" is intended to qualify the amount of a COX-2 inhibiting agent and a topoisomerase II inhibitor required to treat, prevent or inhibit a neoplasia disorder or relieve to some extent or one or more of the symptoms of a neoplasia disorder, including, but not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 4) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 5) inhibition, to some extent, of tumor growth; 6) relieving or reducing to some extent one or more of the symptoms associated with the disorder; or 7) relieving or reducing the side effects associated with the administration of anticancer agents.

[0254] The term "inhibition," in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention.

[0255] The term "prevention," in relation to neoplasia, tumor growth or tumor cell growth, means no tumor or tumor cell growth if none had occurred, no further tumor or tumor cell growth if there had already been growth.

[0256] The term "chemoprevention" refers to the use of agents to arrest or reverse the chronic cancer disease process in its earliest stages before it reaches its terminal invasive and metastatic phase.

[0257] The term "clinical tumor" includes neoplasms that are identifiable through clinical screening or diagnostic procedures including, but not limited to, palpation, biopsy, cell proliferation index, endoscopy, mammagraphy, digital mammography, ultrasonography, computed tomagraphy (CT), magnetic resonance imaging (MRI), positron emission tomagraphy (PET), radiography, radionuclide evaluation, CT- or MRI-guided aspiration cytology, and imaging-guided needle biopsy, among others. Such diagnostic techniques are well known to those skilled in the art and are described in Cancer Medicine 4th Edition, Volume One. J.F. Holland, R.C. Bast, D.L. Morton, E. Frei III, D.W. Kufe, and R.R. Weichselbaum (Editors). Williams & Wilkins, Baltimore (1997).

[0258] The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the COX-2 inhibitor and the topoisomerase II inhibitor or therapy in the combination therapy, defines a quantity of such agent, or a range of quantity of such agent, that is capable of improving the neoplastic disease severity while reducing or avoiding one or more antineoplastic-agent-induced side effects, such as myelosupression, cardiac toxicity, alopecia, nausea or vomiting.

[0259] The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention, including, but not limited to, those agents, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents; agents that prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation; or agents that reduce the incidence of infection associated with the administration of myelosuppressive anticancer drugs.

[0260] The phrase a "device" refers to any appliance, usually mechanical or electrical, designed to perform a particular function.

[0261] The term "angiogenesis" refers to the process by which tumor cells trigger abnormal blood vessel growth to create their own blood supply. Angiogenesis is believed to be the mechanism via which tumors get needed nutrients to grow and metastasize to other locations in the body. Antiangiogenic agents interfere with these processes and destroy or control tumors. Angiogenesis an attractive therapeutic target for treating neoplastic disease because it is a multi-step process that occurs in a specific sequence, thus providing several possible targets for drug action. Examples of agents that interfere with several of these steps include compounds such as matrix metalloproteinase inhibitors (MMPIs) that block the actions of enzymes that clear and create paths for newly forming blood vessels to follow; compounds, such as a_vb_3 inhibitors, that interfere with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor; agents, such as COX-2 selective inhibiting agents, that prevent the growth of cells that form new blood vessels; and protein-based compounds that simultaneously interfere with several of these targets.

[0262] The phrase an "immunotherapeutic agent" refers to agents used to transfer the immunity of an immune donor, e.g., another person or an animal, to a host by inoculation. The term embraces the use of serum or gamma globulin containing performed antibodies produced by another individual or an animal; nonspecific systemic stimulation; adjuvants; active specific immunotherapy; and adoptive immunotherapy. Adoptive immunotherapy refers to the treatment of a disease by therapy or agents that include host inoculation of sensitized lymphocytes, transfer factor, immune RNA, or antibodies in serum or gamma globulin.

[0263] The phrase a "vaccine" includes agents that induce the patient's immune system to mount an immune response against the tumor by attacking cells that express tumor associated antigens (TAAs).

[0264] The phrase "antineoplastic agents" includes agents that exert antineoplastic effects, i.e., prevent the development, maturation, or spread of neoplastic cells, directly on the tumor cell, e.g., by cytostatic or cytocidal effects, and not indirectly through mechanisms such as biological response modification.

[0265] The present invention also provides a method for lowering the risk of a first or subsequent occurrence of a neoplastic disease event comprising the administration of a prophylactically effective amount of a combination of a topoisomerase II inhibitor and a COX-2 inhibiting agent to a patient at risk for such a neoplastic disease event. The patient may already have non-malignant neoplastic disease at the time of administration, or be at risk for developing it.

[0266] Patients to be treated with the present combination therapy includes those at risk of developing neoplastic disease or of having a neoplastic disease event. Standard neoplastic disease risk factors are known to the average physician practicing in the relevant field of medicine. Such known risk factors include but are not limited to genetic factors and exposure to carcinogens such as certain viruses, certain chemicals, tobacco smoke or radiation. Patients who are identified as having one or more risk factors known in the art to be at risk of developing neoplastic disease, as well as people who already have neoplastic disease, are intended to be included within the group of people considered to be at risk for having a neoplastic disease event.

[0267] Studies indicate that prostaglandins synthesized by cyclooxygenases play a critical role in the initiation and

promotion of cancer. Moreover, COX-2 is overexpressed in neoplastic lesions of the colon, breast, lung, prostate, esophagus, pancreas, intestine, cervix, ovaries, urinary bladder, and head and neck. Products of COX-2 activity, i.e., prostaglandins, stimulate proliferation, increase invasiveness of malignant cells, and enhance the production of vascular endothelial growth factor, which promotes angiogenesis. In several in vitro and animal models, COX-2 selective inhibiting agents have inhibited tumor growth and metastasis. The utility of COX-2 selective inhibiting agents as chemopreventive, antiangiogenic and chemotherapeutic agents is described in the literature, see for example Koki et al., Potential utility of COX-2 selective inhibiting agents in chemoprevention and chemotherapy. Exp. Opin. Invest. Drugs (1999) 8(10) pp. 1623-1638.

[0268] In addition to cancers *per se*, COX-2 is also expressed in the angiogenic vasculature within and adjacent to hyperplastic and neoplastic lesions indicating that COX-2 plays a role in angiogenesis. In both the mouse and rat, COX-2 selective inhibiting agents markedly inhibited bFGF-induced neovascularization.

[0269] Also, COX-2 levels are elevated in tumors with amplification and/or overexpression of other oncogenes including but not limited to c-*myc*, N-*myc*, L-*myc*, K-*ras*, H-*ras*, N-*ras*. Consequently, the administration of a COX-2 selective inhibiting agent and a topoisomerase II inhibitor, in combination with an agent, or agents, that inhibits or suppresses oncogenes is contemplated to prevent or treat cancers in which oncogenes are overexpressed.

[0270] Accordingly, there is a need for a method of treating or preventing a cancer in a patient that overexpresses COX-2 or an oncogene.

Dosages, Formulations and Routes of Administration

Dosages

[0271] Dosage levels of the source of a COX-2 inhibiting agent (e.g., a COX-2 selective inhibiting agent or a prodrug of a COX-2 selective inhibiting agent) on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. While the dosage of active compound administered to a warm-blooded animal (a mammal), is dependent on the species of that mammal, the body weight, age, and individual condition, and on the routhe of administration, the unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg of the active ingredient (for example, COX-189). The amount of active ingredient that may be combined with other anticancer agents to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[0272] A total daily dose of a topoisomerase II inhibitor can generally be in the range of from about 0.001 to about 10,000 mg/day in single or divided doses.

[0273] Table No. 9 provides illustrative examples of median dosages for topoisomerase II inhibitors that may be used in combination with a COX-2 inhibitor. It should be noted that specific dose regimen for the chemotherapeutic agents below depends upon dosing considerations based upon a variety of factors including the type of neoplasia; the stage of the neoplasm; the age, weight, sex, and medical condition of the patient; the route of administration; the renal and hepatic function of the patient; and the particular combination employed.

[0274] Table No. 9. Median dosages for selected topoisomerase II inhibitor cancer agents.

CHEMOTHERAPEUTIC AGENT	MEDIAN DOSAGE
Aclarubicin	25 mg/m^2
Amonafide	300 mg/m^2
Amsacrine	30 to 120 mg/m^2
Crisnatol	750 mg/m^2
Epirubicin hydrochloride	100 to 120 mg/m^2
Etoposide	50 to 100 mg/m^2
Daunorubicin	45 mg/m^2
Doxorubicin	60 to 75 mg/m^2
Idarubicin hydrochloride	12 mg/m^2
Mitoxantrone	12 mg/m^2
Pirarubicin	10 to 70 mg/m^2
Sobuzoxane	1600 mg
Teniposide	165 mg/m^2
Valrubicin	800 mg

[0275] It is understood, however, that specific dose levels of the therapeutic agents or therapeutic approaches of the present invention for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the patient, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disease being treated and form of administration.

[0276] Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present invention. In terms of

treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro. Thus, where a compound is found to demonstrate in vitro activity at, e.g., 10 μM, one will desire to administer an amount of the drug that is effective to provide about a 10 μM concentration in vivo. Determination of these parameters is well within the skill of the art.

Formulations and Routes of Administration

[0277] Effective formulations and administration procedures are well known in the art and are described in standard textbooks.

[0278] The COX-2 inhibiting agents or the topoisomerase II inhibitors can be formulated as a single pharmaceutical composition or as independent multiple pharmaceutical compositions. Pharmaceutical compositions according to the present invention include those suitable for oral, inhalation spray, rectal, topical, buccal (e.g., sublingual), or parenteral (e.g., subcutaneous, intramuscular, intravenous, intramedullary and intradermal injections, or infusion techniques) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral or parenteral.

[0279] Compounds and composition of the present invention can then be administered orally, by inhalation spray, rectally, topically, buccally or parenterally in dosage unit formulations containing conventional nontoxic pharmaceutically

acceptable carriers, adjuvants, and vehicles as desired. The compounds of the present invention can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

[0280] The compositions of the present invention can be administered for the prevention or treatment of neoplastic disease or disorders by any means that produce contact of these compounds with their site of action in the body, for example in the ileum, the plasma, or the liver of a mammal.

[0281] Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation.

[0282] The compounds useful in the methods, combinations and compositions of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, consisting essentially of admixing the components.

[0283] The amount of compound in combination that is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific

compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

[0284] The compounds of the present invention can be delivered orally either in a solid, in a semi-solid, or in a liquid form. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the day. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. Capsules, tablets, etc., can be prepared by conventional methods well known in the art. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient or ingredients. Examples of dosage units are tablets or capsules, and may contain one or more therapeutic compounds in an amount described herein. For example, in the case of a topoisomerase II inhibitor, the dose range may be from about 0.01 mg to about 5,000 mg or any other dose, dependent upon the specific inhibitor, as is known in the art. When in a liquid or in a semi-solid form, the combinations of the present invention can, for example, be in the form of a liquid, syrup, or contained in a gel capsule (e.g., a gel cap). In one embodiment, when a topoisomerase II inhibitor is used in a combination of the present invention, the topoisomerase II inhibitor can be provided in the form of a liquid, syrup, or contained in a gel capsule. In another embodiment, when a COX-2 inhibiting agent is used in a combination of the present invention, the COX-2 inhibiting agent can be provided in the form of a liquid, syrup, or contained in a gel capsule.

[0285] Oral delivery of the combinations of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These

include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. For some of the therapeutic compounds useful in the methods, combinations and compositions of the present invention the intended effect is to extend the time period over which the active drug molecule is delivered to the site of action by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

[0286] Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one therapeutic compound useful in the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more assessory ingredients. Compressed tablets can be

prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

[0287] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0288] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[0289] Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection or by infusion. Such preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 10% w/w of a compound disclosed herein.

[0290] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable

preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0291] The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. A suitable daily dose of each active therapeutic compound is one that achieves the same blood serum level as produced by oral administration as described above.

[0292] The dose of any of these therapeutic compounds can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 10,000 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

[0293] Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound or compounds of the present invention with one or more conventional solid carriers, for example, cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt

in the rectum and release the drug; and then shaping the resulting mixture.

[0294] Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include petroleum jelly (e.g., Vaseline), lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound or compounds are generally present at a concentration of from 0.1 to 50% w/w of the composition, for example, from 0.5 to 2%.

[0295] Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound or compounds of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound or compounds is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound or compounds can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

[0296] In any case, the amount of active ingredients that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

[0297] In combination therapy, administration of two or more of the therapeutic agents useful in the methods, combinations and compositions of the present invention may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or in a separate formulation. Independent

administration of each therapeutic agent may be accomplished by, for example, oral, inhalation spray, rectal, topical, buccal (e.g., sublingual), or parenteral (e.g., subcutaneous, intramuscular, intravenous, intramedullary and intradermal injections, or infusion techniques) administration. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. Solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropylmethyl cellulose, together with one or more of a lubricant, preservative, surface active or dispersing agent. The therapeutic compounds may further be administered by any combination of, for example, oral/oral, oral/parenteral, or parenteral/parenteral route.

[0298] The therapeutic compounds which make up the combination therapy may be a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The therapeutic compounds which make up the combination therapy may also be administered sequentially, with either therapeutic compound being administered by a regimen calling for two step ingestion. Thus, a regimen may call for sequential administration of the therapeutic compounds with spaced-apart ingestion of the separate, active agents. The time period between the multiple ingestion steps may range from, for example, a few minutes to several hours to days, depending upon the properties of each therapeutic compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the therapeutic compound, as well as depending upon the effect of food ingestion and the age and condition of the patient. Circadian variation of the target molecule concentration may also determine the optimal dose interval. The therapeutic compounds of the combined therapy whether administered simultaneously, substantially

simultaneously, or sequentially, may involve a regimen calling for administration of one therapeutic compound by oral route and another therapeutic compound by intravenous route. Whether the therapeutic compounds of the combined therapy are administered orally, by inhalation spray, rectally, topically, buccally (e.g., sublingual), or parenterally (e.g., subcutaneous, intramuscular, intravenous and intradermal injections, or infusion techniques), separately or together, each such therapeutic compound will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the therapeutic compounds are given above. Additionally, drug formulations are discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Treatment Regimen

[0299] Any effective treatment regimen can be utilized and readily determined and repeated as necessary to effect treatment. In clinical practice, the compositions containing a COX-2 inhibiting agent in combination with a topoisomerase II inhibitor, (along with other therapeutic agents) are administered in specific cycles until a response is obtained.

[0300] For patients who initially present without advanced or metastatic cancer, a COX-2 inhibiting agent based drug in combination with a topoisomerase II inhibitor will be useful as an immediate initial therapy prior to surgery, chemotherapy, or radiation therapy, and/or as a continuous post-treatment therapy in patients at risk for recurrence or metastasis (for example, in adenocarcinoma of the prostate,

risk for metastasis is based upon high PSA, high Gleason's score, locally extensive disease, and/or pathological evidence of tumor invasion in the surgical specimen). The goal in these patients is to inhibit the growth of potentially metastatic cells from the primary tumor during surgery or radiotherapy and inhibit the growth of tumor cells from undetectable residual primary tumor.

[0301] For patients who initially present with advanced or metastatic cancer, a COX-2 inhibiting agent based drug in combination with a topoisomerase II inhibitor is used as a continuous supplement to, or possible replacement for chemotherapeutic regimes. The goal in these patients is to slow or prevent tumor cell growth from both the untreated primary tumor and from the existing metastatic lesions.

[0302] In addition, the invention may be particularly efficacious during post-surgical recovery, where the present compositions and methods may be particularly effective in lessening the chances of recurrence of a tumor engendered by shed cells that cannot be removed by surgical intervention.

Combinations with Other Treatments

[0303] The methods, combinations and compositions of the present invention may be used in conjunction with other cancer treatment modalities, including, but not limited to surgery and radiation, hormonal therapy, antiangiogenic therapy, chemotherapy, immunotherapy, and cryotherapy. The present invention may be used in conjunction with any current or future therapy.

[0304] The following discussion highlights some agents in this respect, which are illustrative, not limitative. A wide variety of other effective agents also may be used.

Surgery and Radiation

[0305] In general, surgery and radiation therapy are employed as potentially curative therapies for patients under 70 years of age who present with clinically localized disease and are expected to live at least 10 years.

[0306] For example, approximately 70% of newly diagnosed prostate cancer patients fall into this category. Approximately 90% of these patients (65% of total patients) undergo surgery, while approximately 10% of these patients (7% of total patients) undergo radiation therapy. Histopathological examination of surgical specimens reveals that approximately 63% of patients undergoing surgery (40% of total patients) have locally extensive tumors or regional (lymph node) metastasis that was undetected at initial diagnosis. These patients are at a significantly greater risk of recurrence. Approximately 40% of these patients will actually develop recurrence within five years after surgery. Results after radiation are even less encouraging. Approximately 80% of patients who have undergone radiation as their primary therapy have disease persistence or develop recurrence or metastasis within five years after treatment. Currently, most of these surgical and radiotherapy patients generally do not receive any immediate follow-up therapy. Rather, for example, they are monitored frequently for elevated Prostate Specific Antigen ("PSA"), which is the primary indicator of recurrence or metastasis prostate cancer.

[0307] Thus, there is considerable opportunity to use the present invention in conjunction with surgical intervention.

Hormonal Therapy

[0308] Hormonal ablation is the most effective palliative treatment for the 10% of patients presenting with metastatic prostate cancer at initial diagnosis. Hormonal ablation by medication and/or orchiectomy is used to block hormones that

support the further growth and metastasis of prostate cancer. With time, both the primary and metastatic tumors of virtually all of these patients become hormone-independent and resistant to therapy. Approximately 50% of patients presenting with metastatic disease die within three years after initial diagnosis, and 75% of such patients die within five years after diagnosis. Continuous supplementation with NAALADase inhibitor based drugs are used to prevent or reverse this potentially metastasis-permissive state.

[0309] Among hormones which may be used in combination with the present inventive compounds, diethylstilbestrol (DES), leuprolide, flutamide, cyproterone acetate, ketoconazole and amino glutethimide are preferred.

Immunotherapy

[0310] The combinations and methods of the present invention may also be used in combination with monoclonal antibodies in treating cancer. For example monoclonal antibodies may be used in treating prostate cancer. A specific example of such an antibody includes cell membrane-specific anti-prostate antibody.

[0311] The present invention may also be used with immunotherapies based on polyclonal or monoclonal antibody-derived reagents, for instance. Monoclonal antibody-based reagents are most preferred in this regard. Such reagents are well known to persons of ordinary skill in the art. Radiolabelled monoclonal antibodies for cancer therapy, such as the recently approved use of monoclonal antibody conjugated with strontium-89, also are well known to persons of ordinary skill in the art.

Antiangiogenic Therapy

[0312] The combinations and methods of the present invention may also be used in combination with other

antiangiogenic agents in treating cancer. Antiangiogenic agents include but are not limited to MMP inhibitors, integrin antagonists, angiostatin, endostatin, thrombospondin-1, and interferon alpha. Examples of preferred antiangiogenic agents include, but are not limited to vitaxin, marimastat, Bay-12-9566, AG-3340, metastat, EMD-121974, and D-2163 (BMS-275291).

Cryotherapy

[0313] Cryotherapy recently has been applied to the treatment of some cancers. Methods and combinations of the present invention also could be used in conjunction with an effective therapy of this type.

Chemotherapy

[0314] There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be included in the present invention for treatment of neoplasia by combination drug chemotherapy. For convenience of discussion, antineoplastic agents are classified into the following classes, subtypes and species:

ACE inhibitors,
alkylating agents,
angiogenesis inhibitors,
angiostatin,
anthracyclines/DNA intercalators,
anti-cancer antibiotics or antibiotic-type agents,
antimetabolites,
antimetastatic compounds,
asparaginases,
bisphosphonates,
cGMP phosphodiesterase inhibitors,
calcium carbonate,
COX-2 inhibitors

DHA derivatives,
DNA topoisomerase,
endostatin,
epipodophylotoxins,
genistein,
hormonal anticancer agents,
hydrophilic bile acids (URSO),
immunomodulators or immunological agents,
integrin antagonists
interferon antagonists or agents,
MMP inhibitors,
miscellaneous antineoplastic agents,
monoclonal antibodies,
nitrosoureas,
NSAIDs,
ornithine decarboxylase inhibitors,
pBATTs,
radio/chemo sensitizers/protectors,
retinoids
selective inhibitors of proliferation and migration of endothelial cells,
selenium,
stromelysin inhibitors,
taxanes,
vaccines, and
vinca alkaloids.

The major categories that some preferred antineoplastic agents fall into include antimetabolite agents, alkylating agents, antibiotic-type agents, hormonal anticancer agents, immunological agents, interferon-type agents, and a category of miscellaneous antineoplastic agents. Some antineoplastic agents operate through multiple or unknown mechanisms and can thus be classified into more than one category.

Therapeutic Illustrations

[0315] All of the various cell types of the body can be transformed into benign or malignant neoplasia or tumor cells and are contemplated as objects of the invention. A "benign" tumor cell denotes the non-invasive and non-metastasized state of a neoplasm. In man the most frequent neoplasia site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia, central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer. The following non-limiting illustrative examples describe various cancer diseases and therapeutic approaches that may be used in the present invention, and are for illustrative purposes only. Some COX-2 inhibiting agents (or prodrugs thereof) that will be useful in the below non-limiting illustrations include, but are not limited to celecoxib, deracoxib, parecoxib, chromene COX-2 inhibitors, valdecoxib, rofecoxib, etoricoxib, meloxicam, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, diarylmethylidenefuran derivative COX-2 inhibitors, and BMS 347070 or other similar compounds. Some topoisomerase II inhibitors that will be useful with the below non-limiting illustrations include, for example, aclarubicin, amonafide, amrubicin, amsacrine, crisnatol, daunorubicin, doxorubicin, epirubicin, etoposide, idarubicin, mitoxantrone, nemorubicin, pirarubicin, sobuzoxane, teniposide, and valrubicin.

Illustration 1: Lung Cancer

[0316] In many countries including Japan, Europe and America, the number of patients with lung cancer is fairly large and continues to increase year after year and is the most frequent cause of cancer death in both men and women. Although there are many potential causes for lung cancer, tobacco use, and particularly cigarette smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in smokers, or radon are contributory factors. Also occupational hazards such as exposure to uranium have been identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of cancer.

[0317] Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell lung cancer (oat cell). Non-small cell lung cancer (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell lung cancer (SCLC). Thus, chemotherapeutic formulas and radiation therapy are different between these two types of lung cancer.

Non-Small Cell Lung Cancer

[0318] In the present invention, a preferred therapy for the treatment of NSCLC is a combination of neoplasia disorder effective amounts of a COX-2 inhibitor in combination with one or more of the following combinations of antineoplastic agents: 1) ifosfamide, cisplatin, etoposide; 2) cyclophosphamide, doxorubicin, cisplatin; 3) ifosfamide, carboplatin, etoposide; 4) bleomycin, etoposide, cisplatin; 5) ifosfamide, etoposide; 6) etoposide, cisplatin; 7) carboplatin, etoposide; or radiation therapy.

Small Cell Lung Cancer

[0319] In another embodiment of the present invention, a preferred therapy for the treatment of lung cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibitor in combination with the following antineoplastic agents: epirubicin (high dose), etoposide (VP-16) I.V., etoposide (VP-16) oral, teniposide (VM-26), and doxorubicin.

[0320] A further preferred therapy for the treatment of SCLC in the present invention is a combination of neoplasia disorder effective amounts of a COX-2 inhibitor in combination with the following combinations of antineoplastic agents: 1) etoposide (VP-16), cisplatin; 2) cyclophosphamide, adrianmycin [(doxorubicin), vincristine, etoposide (VP-16)]; 3) cyclophosphamide, adrianmycin (doxorubicin), vincristine; 4) etoposide (VP-16), ifosfamide, cisplatin; 5) etoposide (VP-16), carboplatin; 6) cisplatin, vincristine (Oncovin), doxorubicin, etoposide.

[0321] Additionally, radiation therapy in conjunction with the preferred combinations of neoplasia disorder effective amounts of a COX-2 inhibitor and a topoisomerase II inhibitor is contemplated to be effective at increasing the response rate for SCLC patients. The typical dosage regimen for radiation therapy ranges from 40 to 55 Gy, in 15 to 30 fractions, 3 to 7 times week. The tissue volume to be irradiated will be determined by several factors and generally the hilum and subcarnial nodes, and bialteral mdiastinal nodes up to the thoraic inlet are treated, as well as the primary tumor up to 1.5 to 2.0 cm of the margins.

Illustration 2: Colorectal Cancer

[0322] Tumor metastasis prior to surgery is generally believed to be the cause of surgical intervention failure and up to one year of chemotherapy is required to kill the non-excised tumor cells. Because severe toxicity is associated

with the chemotherapeutic agents, only patients at high risk of recurrence are placed on chemotherapy following surgery. Thus, the incorporation of a COX-2 inhibitor and a topoisomerase II inhibitor into the management of colorectal cancer will play an important role in the treatment of colorectal cancer and lead to overall improved survival rates for patients diagnosed with colorectal cancer.

[0323] In one embodiment of the present invention, a combination therapy for the treatment of colorectal cancer is surgery, followed by a regimen of a COX-2 inhibiting agent and a topoisomerase II inhibitor, cycled over a one year time period. In another embodiment, a combination therapy for the treatment of colorectal cancer is a regimen of a COX-2 inhibiting agent and a topoisomerase II inhibitor, followed by surgical removal of the tumor from the colon or rectum and then followed be a regimen of a COX-2 inhibiting agent and a topoisomerase II inhibitor, cycled over a one year time period. In still another embodiment, a therapy for the treatment of colon cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor.

[0324] In another embodiment of the present invention, a therapy for the treatment of colon cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor in combination with fluorouracil and Levamisole. Typically, fluorouracil and Levamisole are used in combination.

Illustration 3: Breast Cancer

[0325] In the treatment of locally advanced noninflammatory breast cancer, a COX-2 inhibiting agent and a topoisomerase II inhibitor will be useful to treat the disease in combination with surgery, radiation therapy and/or chemotherapy. Combinations of chemotherapeutic agents,

radiation therapy and surgery that will be useful in combination with the present invention include, but are not limited to the following combinations: 1) doxorubicin, vincristine, radical mastectomy; 2) doxorubicin, vincristine, radiation therapy; 3) cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone, mastectomy; 4) cyclophosphamide, doxorubicin, 5-flourouracil, vincristine, prednisone, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, radiation therapy for pathologic complete response; 6) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, mastectomy, radiation therapy for pathologic partial response; 7) mastectomy, radiation therapy; 8) mastectomy, vincristine, doxorubicin, cyclophosphamide, levamisole; 9) mastectomy, vincristine, doxorubicin, cyclophosphamide; 10) mastectomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin, radiation therapy; 11) mastectomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin.

[0326] In the treatment of locally advanced inflammatory breast cancer, a COX-2 inhibiting agent and a topoisomerase II inhibitor will be useful to treat the disease in combination with surgery, radiation therapy or with chemotherapeutic agents. In one embodiment combinations of chemotherapeutic agents, radiation therapy and surgery that will be useful in combination with a COX-2 inhibiting agent include, but are not limited to the following combinations: 1) cyclophosphamide, doxorubicin, 5-fluorouracil, radiation therapy; 2) cyclophosphamide, doxorubicin, 5-fluorouracil, mastectomy, radiation therapy; 3) 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, prednisone, mastectomy, radiation therapy; 4) 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, mastectomy, radiation therapy; 5) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine,

radiation therapy; 6) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, mastectomy, radiation therapy; 7) doxorubicin, vincristine, methotrexate, radiation therapy, followed by vincristine, cyclophosphamide, 5-florouracil; 8) doxorubicin, vincristine, cyclophosphamide, methotrexate, 5-florouracil, radiation therapy, followed by vincristine, cyclophosphamide, 5-florouracil; 9) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 10) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 11) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine, tamoxifen;; 12) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine; 13) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine, tamoxifen; 14) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, doxorubicin, vincristine; 15) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, followed by radiation therapy, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine; 16) 5-

florouracil, doxorubicin, cyclophosphamide followed by mastectomy, followed by 5-florouracil, doxorubicin, cyclophosphamide, followed by radiation therapy.

[0327] In the treatment of metastatic breast cancer, a COX-2 inhibiting agent and a topoisomerase II inhibitor will be useful to treat the disease in combination with surgery, radiation therapy and/or with chemotherapeutic agents. In one embodiment, combinations of chemotherapeutic agents that will be useful in combination with a COX-2 inhibiting agent and a topoisomerase II inhibitor of the present invention, include, but are not limited to the following combinations: 1) cyclophosphamide, methotrexate, 5-fluorouracil; 2) cyclophosphamide, adriamycin, 5-fluorouracil; 3) cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone; 4) adriamycin, vincristine; 5) thiotepa, adriamycin, vinblastine; 6) mitomycin, vinblastine; 7) cisplatin, etoposide. In another embodiment, combinations of chemotherapeutic agents that will be useful in combination with a COX-2 inhibiting agent, include, but are not limited to the following combinations: 1) fluorouracil, epirubicin, and cyclophosphamide; and 2) fluorouracil, doxorubicin, and cyclophosphamide.

Illustration 4: Prostate Cancer

[0328] In one embodiment of the present invention, a therapy for the treatment of prostate cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor. A preferred combination for the treatment of prostate cancer is a COX-2 inhibitor and epirubicin. Another preferred combination for the treatment of prostate cancer is a COX-2 inhibitor, epirubicin and docetaxel.

Illustration 5: Bladder Cancer

[0329] The classification of bladder cancer is divided into three main classes: 1) superficial disease, 2) muscle-invasive disease, and 3) metastatic disease.

[0330] Currently, transurethral resection (TUR), or segmental resection, account for first line therapy of superficial bladder cancer, i.e., disease confined to the mucosa or the lamina propria. However, intravesical therapies are necessary, for example, for the treatment of high-grade tumors, carcinoma in situ, incomplete resections, recurrences, and multifocal papillary. Recurrence rates range from up to 30 to 80 percent, depending on stage of cancer.

[0331] Therapies that are currently used as intravesical therapies include chemotherapy, immuontherapy, bacille Calmette-Guerin (BCG) and photodynamic therapy. The main objective of intravesical therapy is twofold: to prevent recurrence in high-risk patients and to treat disease that cannot be resected. The use of intravesical therapies must be balanced with its potentially toxic side effects. Additionally, BCG requires an unimpaired immune system to induce an antitumor effect. Chemotherapeutic agents that are known to be of limited use against superficial bladder cancer include cisplatin, actinomycin D, 5-fluorouracil, bleomycin, cyclophosphamide and methotrexate.

[0332] In the treatment of superficial bladder cancer, a COX-2 inhibiting agent and a topoisomerase II inhibitor will be useful to treat the disease in combination with surgery (TUR), chemotherapy and/or intravesical therapies.

[0333] A therapy for the treatment of superficial bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with doxorubicin (20 to 80 mg/day) or epirubicin (30 to 80 mg/day), following surgery (TUR).

[0334] In one embodiment, an intravesicle immunotherapeutic agent that may be used in the methods, combinations and compositions of the present invention is BCG. A daily dose ranges from 60 to 120 mg, depending on the strain of the live attenuated tuberculosis organism used.

[0335] In another embodiment, a photodynamic therapeutic agent that may be used with the present invention is Photofrin I, a photosensitizing agent, administered intravenously. It is taken up by the low-density lipoprotein receptors of the tumor cells and is activated by exposure to visible light. Additionally, neomydium YAG laser activation generates large amounts of cytotoxic free radicals and singlet oxygen.

[0336] In the treatment of muscle-invasive bladder cancer, a COX-2 inhibiting agent and a topoisomerase II inhibitor will be useful to treat the disease in combination with surgery (TUR), intravesical chemotherapy, radiation therapy, and/or radical cystectomy with pelvic lymph node dissection.

[0337] In one embodiment of the present invention, the radiation dose for the treatment of bladder cancer is between 5,000 to 7,000 cGY in fractions of 180 to 200 cGY to the tumor. Additionally, 3,500 to 4,700 cGY total dose is administered to the normal bladder and pelvic contents in a four-field technique. Radiation therapy should be considered only if the patient is not a surgical candidate, but may be considered as preoperative therapy.

[0338] In another embodiment of the present invention, a combination of surgery and chemotherapeutic agents that will be useful in combination with a COX-2 inhibiting agent is cystectomy in conjunction with five cycles of cisplatin (70 to 100 mg/m(square)); doxorubicin (50 to 60 mg/m(square); and cyclophosphamide (500 to 600 mg/m(square).

[0339] In one embodiment of the present invention, a therapy for the treatment of superficial bladder cancer is a

combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor.

[0340] In another embodiment of the present invention, a combination for the treatment of superficial bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; and 2) cisplatin, 5-fluorouracil. A combination of chemotherapeutic agents that will be useful in combination with radiation therapy, a COX-2 inhibiting agent and a topoisomerase II inhibitor is a combination of cisplatin, methotrexate, vinblastine.

[0341] Currently no curative therapy exists for metastatic bladder cancer. The present invention contemplates an effective treatment of bladder cancer leading to improved tumor inhibition or regression, as compared to current therapies. In the treatment of metastatic bladder cancer, a COX-2 inhibiting agent and a topoisomerase II inhibitor will be useful to treat the disease in combination with surgery, radiation therapy and/or with chemotherapeutic agents.

[0342] In one embodiment of the present invention, a therapy for the treatment of metastatic bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor. In another embodiment of the present invention, therapy for the treatment of metastatic bladder cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with one or more of the following combinations of antineoplastic agents: 1) doxorubicin, vinblastine, cyclophosphamide, and 5-fluorouracil; 2) vinblastine, doxorubicin, cisplatin, methotrexate; and 3) cyclophosphamide, doxorubicin, cisplatin.

<u>Illustration 6: Pancreas Cancer</u>

[0343] Approximately 2% of new cancer cases diagnosed in the United States are pancreatic cancer. Pancreatic cancer is generally classified into two clinical types: 1) adenocarcinoma (metastatic and non-metastatic), and 2) cystic neoplasms (serous cystadenomas, mucinous cystic neoplasms, papillary cystic neoplasms, acinar cell systadenocarcinoma, cystic choriocarcinoma, cystic teratomas, angiomatous neoplasms).

[0344] In one embodiment, a therapy for the treatment of non-metastatic adenocarcinoma that may be used in the methods, combinations and compositions of the present invention include the use of a COX-2 inhibiting agent and a topoisomerase II inhibitor along with preoperative biliary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant radiation; and/or chemotherapy.

[0345] In one embodiment for the treatment of metastatic adenocarcinoma, a therapy consists of a COX-2 inhibiting agent and a topoisomerase II inhibitor of the present invention in combination with continuous treatment of 5- fluorouracil, followed by weekly cisplatin therapy.

[0346] In another embodiment of the present invention, a combination therapy for the treatment of cystic neoplasms is the use of a COX-2 inhibiting agent and a topoisomerase II inhibitor along with resection.

Illustration 7: Ovary Cancer

[0347] Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. In one embodiment of the present invention, a therapy for the treatment of ovary cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor.

[0348] Single agents that will be useful in combination with a COX-2 inhibiting agent and a topoisomerase II inhibitor include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, and prednimustine.

[0349] In another embodiment of the present invention, combinations for the treatment of celomic epithelial carcinoma are a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamethylmelamine, cyclophosphamide, doxorubicin, cisplatin; 3) melphalan, doxorubicin, cyclophosphamide; 4) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 5) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 6) hexamethylmelamine, doxorubicin, carboplatin; and 7) cyclophosphamide, hexamethylmelamine, doxorubicin, cisplatin.

[0350] Germ cell ovarian cancer accounts for approximately 5% of ovarian cancer cases. Germ cell ovarian carcinomas are classified into two main groups: 1) dysgerminoma, and nondysgerminoma. Nondysgerminoma is further classified into teratoma, endodermal sinus tumor, embryonal carcinoma, chloricarcinoma, polyembryoma, and mixed cell tumors.

[0351] In one embodiment of the present invention, a therapy for the treatment of germ cell carcinoma is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor.

[0352] In another embodiment of the present invention, a therapy for the treatment of germ cell carcinoma is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with the following combination of antineoplastic agents: bleomycin, etoposide, cisplatin.

[0353] Cancer of the fallopian tube is the least common type of ovarian cancer, accounting for approximately 400 new cancer cases per year in the United States. Papillary serous adenocarcinoma accounts for approximately 90% of all malignancies of the ovarian tube.

[0354] In one embodiment of the present invention, a therapy for the treatment of fallopian tube cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor.

[0355] In another embodiment of the present invention, a therapy for the treatment of fallopian tube cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with doxorubicin

[0356] In still another embodiment of the present invention, therapy for the treatment of fallopian tube cancer is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with one or more of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclophosphamide, doxorubicin, cisplatin; 4) melphalan, doxorubicin, cyclophosphamide; 5) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 6) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 7) hexamethylmelamine, doxorubicin, carboplatin; and 8) cyclophosphamide, hexamethylmelamine, doxorubicin, cisplatin.

Illustration 8: Central Nervous System Cancers

[0357] Central nervous system cancer accounts for approximately 2% of new cancer cases in the United States. Common intracranial neoplasms include glioma, meninigioma, neurinoma, and adenoma.

[0358] In one embodiment of the present invention, a therapy for the treatment of central nervous system cancers is

a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor.

[0359] In another embodiment of the present invention, a therapy for the treatment of malignant glioma. is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent and a topoisomerase II inhibitor in combination with one or more of the following combinations of therapies and antineoplastic agents: 1) radiation therapy, BCNU (carmustine); 2) radiation therapy, methyl CCNU (lomustine); 3) radiation therapy, medol; 4) radiation therapy, procarbazine; 5) radiation therapy, BCNU, medrol; 6) hyperfraction radiation therapy, BCNU; 7) radiation therapy, misonidazole, BCNU; 8) radiation therapy, streptozotocin; 9) radiation therapy, BCNU, procarbazine; 10) radiation therapy, BCNU, hydroxyurea, procarbazine, VM-26; 11) radiation therapy, BNCU, 5-flourouacil; 12) radiation therapy, Methyl CCNU, dacarbazine; 13) radiation therapy, misonidazole, BCNU; 14) diaziquone; 15) radiation therapy, PCNU; 16) procarbazine (matulane), CCNU, vincristine. In yet another embodiment of the present invention, a therapy for the treatment of malignant glioma is a combination of neoplasia disorder effective amounts of a COX-2 inhibiting agent in combination with radiation therapy, BCNU, hydroxyurea, procarbazine, and VM-26. A dose of radiation therapy is about 5,500 to about 6,000 cGY. Radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR). It is also contemplated that radiosurgery may be used in combinations with a COX-2 inhibiting agent and a topoisomerase II inhibitor.

Illustration 9

[0360] Table No. 10 provides additional non-limiting illustrative examples of combination therapies that will be

useful in the methods, combinations and compositions of the present invention.

[0361] Table No. 10. Combination therapy examples

COX-2 Inhibitor	Antineoplastic Agents	Indication
Celecoxib	Etoposide	Lung
Rofecoxib	Etoposide	Lung
JTE-522	Etoposide	Lung
Valdecoxib	Etoposide	Lung
Parecoxib	Etoposide	Lung
Etoricoxib	Etoposide	Lung

[0362] Additional examples of combinations are listed in Table No 11.

[0363] Table No. 11. Combination therapy examples

COX-2 Inhibitor	Antineoplastic Agents	Indication
Celecoxib	Doxorubicin and Cyclophosphamide	Breast
Celecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Celecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Celecoxib	Vinblastine,Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Celecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast

COX-2 Inhibitor	Antineoplastic Agents	Indication
Celecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Celecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Celecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Celecoxib	Etoposide, Carboplatin	Lung
Celecoxib	Etoposide, Cisplatin	Lung
Rofecoxib	Doxorubicin and Cyclophosphamide	Breast
Rofecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Rofecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Rofecoxib	Vinblastine,Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Rofecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast

COX-2 Inhibitor	Antineoplastic Agents	Indication
Rofecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Rofecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Rofecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Rofecoxib	Etoposide, Carboplatin	Lung
Rofecoxib	Etoposide, Cisplatin	Lung
JTE-522	Doxorubicin and Cyclophosphamide	Breast
JTE-522	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
JTE-522	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
JTE-522	Vinblastine,Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
JTE-522	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast

COX-2 Inhibitor	**Antineoplastic Agents**	**Indication**
JTE-522	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
JTE-522	Cyclophosphamide, Doxorubicin, Etoposide	Lung
JTE-522	Cyclophosphamide, Doxorubicin, Vincristine	Lung
JTE-522	Etoposide, Carboplatin	Lung
JTE-522	Etoposide, Cisplatin	Lung
Valdecoxib	Doxorubicin and Cyclophosphamide	Breast
Valdecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Valdecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Valdecoxib	Vinblastine,Doxoru bicin, Thiotepa, and Fluoxymestrone	Breast
Valdecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast

COX-2 Inhibitor	Antineoplastic Agents	Indication
Valdecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Valdecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Valdecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Valdecoxib	Etoposide, Carboplatin	Lung
Valdecoxib	Etoposide, Cisplatin	Lung
Parecoxib	Doxorubicin and Cyclophosphamide	Breast
Parecoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Parecoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Parecoxib	Vinblastine,Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Parecoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast

COX-2 Inhibitor	Antineoplastic Agents	Indication
Parecoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Parecoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Parecoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Parecoxib	Etoposide, Carboplatin	Lung
Parecoxib	Etoposide, Cisplatin	Lung
Etoricoxib	Doxorubicin and Cyclophosphamide	Breast
Etoricoxib	Cyclophosphamide, Doxorubicin, and Fluorouracil	Breast
Etoricoxib	Cyclophosphamide, Fluorouracil and Mitoxantrone	Breast
Etoricoxib	Vinblastine,Doxorubicin, Thiotepa, and Fluoxymestrone	Breast
Etoricoxib	Doxorubicin, Cyclophosphamide, Methotrexate, Fluorouracil	Breast

COX-2 Inhibitor	Antineoplastic Agents	Indication
Etoricoxib	Vinblastine, Doxorubicin, Thiotepa, Fluoxymesterone	Breast
Etoricoxib	Cyclophosphamide, Doxorubicin, Etoposide	Lung
Etoricoxib	Cyclophosphamide, Doxorubicin, Vincristine	Lung
Etoricoxib	Etoposide, Carboplatin	Lung
Etoricoxib	Etoposide, Cisplatin	Lung

Illustration 10

[0364] Table 12 illustrates examples of some combinations of the present invention wherein the combination comprises an amount of a COX-2 selective inhibitor source and an amount of a topoisomerase II inhibitor wherein the amounts together comprise a neoplasia disorder effective amount of the compounds.

[0365] Table No. 12. Combinations of COX-2 selective inhibiting agents and topoisomerase II inhibitors.

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
1	C1	T1
2	C1	T2
3	C1	T3
4	C1	T4

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
5	C1	T5
6	C1	T6
7	C1	T7
8	C1	T8
9	C1	T9
10	C1	T10
11	C1	T11
12	C1	T12
13	C1	T13
14	C1	T14
15	C1	T15
16	C1	T16
17	C1	T17
18	C1	T18
19	C1	T19
20	C1	T20
21	C1	T21
22	C1	T22
23	C1	T23
24	C1	T24
25	C1	T25
26	C1	T26
27	C1	T27
28	C1	T28
29	C1	T29
30	C1	T30
31	C1	T31
32	C1	T32
33	C1	T33
34	C1	T34
35	C1	T35

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
36	C1	T36
37	C1	T37
38	C1	T38
39	C1	T39
40	C2	T1
41	C2	T2
42	C2	T3
43	C2	T4
44	C2	T5
45	C2	T6
46	C2	T7
47	C2	T8
48	C2	T9
49	C2	T10
50	C2	T11
51	C2	T12
52	C2	T13
53	C2	T14
54	C2	T15
55	C2	T16
56	C2	T17
57	C2	T18
58	C2	T19
59	C2	T20
60	C2	T21
61	C2	T22
62	C2	T23
63	C2	T24
64	C2	T25
65	C2	T26
66	C2	T27

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
67	C2	T28
68	C2	T29
69	C2	T30
70	C2	T31
71	C2	T32
72	C2	T33
73	C2	T34
74	C2	T35
75	C2	T36
76	C2	T37
77	C2	T38
78	C2	T39
79	C3	T1
80	C3	T2
81	C3	T3
82	C3	T4
83	C3	T5
84	C3	T6
85	C3	T7
86	C3	T8
87	C3	T9
88	C3	T10
89	C3	T11
90	C3	T12
91	C3	T13
92	C3	T14
93	C3	T15
94	C3	T16
95	C3	T17
96	C3	T18
97	C3	T19

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
98	C3	T20
99	C3	T21
100	C3	T22
101	C3	T23
102	C3	T24
103	C3	T25
104	C3	T26
105	C3	T27
106	C3	T28
107	C3	T29
108	C3	T30
109	C3	T31
110	C3	T32
111	C3	T33
112	C3	T34
113	C3	T35
114	C3	T36
115	C3	T37
116	C3	T38
117	C3	T39
118	C4	T1
119	C4	T2
120	C4	T3
121	C4	T4
122	C4	T5
123	C4	T6
124	C4	T7
125	C4	T8
126	C4	T9
127	C4	T10
128	C4	T11

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
129	C4	T12
130	C4	T13
131	C4	T14
132	C4	T15
133	C4	T16
134	C4	T17
135	C4	T18
136	C4	T19
137	C4	T20
138	C4	T21
139	C4	T22
140	C4	T23
141	C4	T24
142	C4	T25
143	C4	T26
144	C4	T27
145	C4	T28
146	C4	T29
147	C4	T30
148	C4	T31
149	C4	T32
150	C4	T33
151	C4	T34
152	C4	T35
153	C4	T36
154	C4	T37
155	C4	T38
156	C4	T39
157	C5	T1
158	C5	T2
159	C5	T3

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
160	C5	T4
161	C5	T5
162	C5	T6
163	C5	T7
164	C5	T8
165	C5	T9
166	C5	T10
167	C5	T11
168	C5	T12
169	C5	T13
170	C5	T14
171	C5	T15
172	C5	T16
173	C5	T17
174	C5	T18
175	C5	T19
176	C5	T20
177	C5	T21
178	C5	T22
179	C5	T23
180	C5	T24
181	C5	T25
182	C5	T26
183	C5	T27
184	C5	T28
185	C5	T29
186	C5	T30
187	C5	T31
188	C5	T32
189	C5	T33
190	C5	T34

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
191	C5	T35
192	C5	T36
193	C5	T37
194	C5	T38
195	C5	T39
196	C6	T1
197	C6	T2
198	C6	T3
199	C6	T4
200	C6	T5
201	C6	T6
202	C6	T7
203	C6	T8
204	C6	T9
205	C6	T10
206	C6	T11
207	C6	T12
208	C6	T13
209	C6	T14
210	C6	T15
211	C6	T16
212	C6	T17
213	C6	T18
214	C6	T19
215	C6	T20
216	C6	T21
217	C6	T22
218	C6	T23
219	C6	T24
220	C6	T25
221	C6	T26

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
222	C6	T27
223	C6	T28
224	C6	T29
225	C6	T30
226	C6	T31
227	C6	T32
228	C6	T33
229	C6	T34
230	C6	T35
231	C6	T36
232	C6	T37
233	C6	T38
234	C6	T39
235	C7	T1
236	C7	T2
237	C7	T3
238	C7	T4
239	C7	T5
240	C7	T6
241	C7	T7
242	C7	T8
243	C7	T9
244	C7	T10
245	C7	T11
246	C7	T12
247	C7	T13
248	C7	T14
249	C7	T15
250	C7	T16
251	C7	T17
252	C7	T18

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
253	C7	T19
254	C7	T20
255	C7	T21
256	C7	T22
257	C7	T23
258	C7	T24
259	C7	T25
260	C7	T26
261	C7	T27
262	C7	T28
263	C7	T29
264	C7	T30
265	C7	T31
266	C7	T32
267	C7	T33
268	C7	T34
269	C7	T35
270	C7	T36
271	C7	T37
272	C7	T38
273	C7	T39
274	C23	T1
275	C23	T2
276	C23	T3
277	C23	T4
278	C23	T5
279	C23	T6
280	C23	T7
281	C23	T8
282	C23	T9
283	C23	T10

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
284	C23	T11
285	C23	T12
286	C23	T13
287	C23	T14
288	C23	T15
289	C23	T16
290	C23	T17
291	C23	T18
292	C23	T19
293	C23	T20
294	C23	T21
295	C23	T22
296	C23	T23
297	C23	T24
298	C23	T25
299	C23	T26
300	C23	T27
301	C23	T28
302	C23	T29
303	C23	T30
304	C23	T31
305	C23	T32
306	C23	T33
307	C23	T34
308	C23	T35
309	C23	T36
310	C23	T37
311	C23	T38
312	C23	T39
313	C44	T1
314	C44	T2

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
315	C44	T3
316	C44	T4
317	C44	T5
318	C44	T6
319	C44	T7
320	C44	T8
321	C44	T9
322	C44	T10
323	C44	T11
324	C44	T12
325	C44	T13
326	C44	T14
327	C44	T15
328	C44	T16
329	C44	T17
330	C44	T18
331	C44	T19
332	C44	T20
333	C44	T21
334	C44	T22
335	C44	T23
336	C44	T24
337	C44	T25
338	C44	T26
339	C44	T27
340	C44	T28
341	C44	T29
342	C44	T30
343	C44	T31
344	C44	T32
345	C44	T33

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
346	C44	T34
347	C44	T35
348	C44	T36
349	C44	T37
350	C44	T38
351	C44	T39
352	C46	T1
353	C46	T2
354	C46	T3
355	C46	T4
356	C46	T5
357	C46	T6
358	C46	T7
359	C46	T8
360	C46	T9
361	C46	T10
362	C46	T11
363	C46	T12
364	C46	T13
365	C46	T14
366	C46	T15
367	C46	T16
368	C46	T17
369	C46	T18
370	C46	T19
371	C46	T20
372	C46	T21
373	C46	T22
374	C46	T23
375	C46	T24
376	C46	T25

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
377	C46	T26
378	C46	T27
379	C46	T28
380	C46	T29
381	C46	T30
382	C46	T31
383	C46	T32
384	C46	T33
385	C46	T34
386	C46	T35
387	C46	T36
388	C46	T37
389	C46	T38
390	C46	T39
391	C66	T1
392	C66	T2
393	C66	T3
394	C66	T4
395	C66	T5
396	C66	T6
397	C66	T7
398	C66	T8
399	C66	T9
400	C66	T10
401	C66	T11
402	C66	T12
403	C66	T13
404	C66	T14
405	C66	T15
406	C66	T16
407	C66	T17

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
408	C66	T18
409	C66	T19
410	C66	T20
411	C66	T21
412	C66	T22
413	C66	T23
414	C66	T24
415	C66	T25
416	C66	T26
417	C66	T27
418	C66	T28
419	C66	T29
420	C66	T30
421	C66	T31
422	C66	T32
423	C66	T33
424	C66	T34
425	C66	T35
426	C66	T36
427	C66	T37
428	C66	T38
429	C66	T39
430	C67	T1
431	C67	T2
432	C67	T3
433	C67	T4
434	C67	T5
435	C67	T6
436	C67	T7
437	C67	T8
438	C67	T9

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
439	C67	T10
440	C67	T11
441	C67	T12
442	C67	T13
443	C67	T14
444	C67	T15
445	C67	T16
446	C67	T17
447	C67	T18
448	C67	T19
449	C67	T20
450	C67	T21
451	C67	T22
452	C67	T23
453	C67	T24
454	C67	T25
455	C67	T26
456	C67	T27
457	C67	T28
458	C67	T29
459	C67	T30
460	C67	T31
461	C67	T32
462	C67	T33
463	C67	T34
464	C67	T35
465	C67	T36
466	C67	T37
467	C67	T38
468	C67	T39

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
469	a chromene COX-2 inhibitor	T1
470	a chromene COX-2 inhibitor	T2
471	a chromene COX-2 inhibitor	T3
472	a chromene COX-2 inhibitor	T4
473	a chromene COX-2 inhibitor	T5
474	a chromene COX-2 inhibitor	T6
475	a chromene COX-2 inhibitor	T7
476	a chromene COX-2 inhibitor	T8
477	a chromene COX-2 inhibitor	T9
478	a chromene COX-2 inhibitor	T10
479	a chromene COX-2 inhibitor	T11
480	a chromene COX-2 inhibitor	T12
481	a chromene COX-2 inhibitor	T13
482	a chromene COX-2 inhibitor	T14
483	a chromene COX-2 inhibitor	T15
484	a chromene COX-2 inhibitor	T16

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
485	a chromene COX-2 inhibitor	T17
486	a chromene COX-2 inhibitor	T18
487	a chromene COX-2 inhibitor	T19
488	a chromene COX-2 inhibitor	T20
489	a chromene COX-2 inhibitor	T21
490	a chromene COX-2 inhibitor	T22
491	a chromene COX-2 inhibitor	T23
492	a chromene COX-2 inhibitor	T24
493	a chromene COX-2 inhibitor	T25
494	a chromene COX-2 inhibitor	T26
495	a chromene COX-2 inhibitor	T27
496	a chromene COX-2 inhibitor	T28
497	a chromene COX-2 inhibitor	T29
498	a chromene COX-2 inhibitor	T30
499	a chromene COX-2 inhibitor	T31
500	a chromene COX-2 inhibitor	T32

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
501	a chromene COX-2 inhibitor	T33
502	a chromene COX-2 inhibitor	T34
503	a chromene COX-2 inhibitor	T35
504	a chromene COX-2 inhibitor	T36
505	a chromene COX-2 inhibitor	T37
506	a chromene COX-2 inhibitor	T38
507	a chromene COX-2 inhibitor	T39
508	C68	T1
509	C68	T2
510	C68	T3
511	C68	T4
512	C68	T5
513	C68	T6
514	C68	T7
515	C68	T8
516	C68	T9
517	C68	T10
518	C68	T11
519	C68	T12
520	C68	T13
521	C68	T14
522	C68	T15
523	C68	T16
524	C68	T17

Example Number	COX-2 Inhibitor	Topoisomerase II Inhibitor
525	C68	T18
526	C68	T19
527	C68	T20
528	C68	T21
529	C68	T22
530	C68	T23
531	C68	T24
532	C68	T25
533	C68	T26
534	C68	T27
535	C68	T28
536	C68	T29
537	C68	T30
538	C68	T31
539	C68	T32
540	C68	T33
541	C68	T34
542	C68	T35
543	C68	T36
544	C68	T37
545	C68	T38
546	C68	T39

Biological Assays

Evaluation of COX-1 and COX-2 activity *in vitro*

[0366] The COX-2 inhibiting agents of this invention exhibit inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds illustrated in the examples above are determined by the following methods. The COX-2 inhibition

activity of the other COX-2 inhibitors of the present invention may also be determined by the following methods.

Preparation of recombinant COX baculoviruses

[0367] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 μg of baculovirus transfer vector DNA into SF9 insect cells (2x108) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (107-108 pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

Assay for COX-1 and COX-2 activity

[0368] COX activity is assayed as PGE2 formed/μg protein/time using an ELISA to detect the prostaglandin

released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 μM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C/room temperature by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

Fast assay for COX-1 and COX-2 activity

[0369] COX activity is assayed as PGE2 formed/μg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 μM phenol, 1 μM heme, 300 μM epinephrine) with the addition of 20 μl of 100 μM arachidonic acid (10 μM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C/room temperature by transferring 40 μl of reaction mix into 160 μl ELISA buffer and 25 μM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

Biological Evaluation

[0370] A combination therapy of a COX-2 inhibiting agent and a topoisomerase II inhibitor for the treatment or prevention of a neoplasia disorder in a mammal can be evaluated as described in the following tests.

Lewis Lung Model

[0371] Mice are injected subcutaneously in the left paw (1×10^6 tumor cells suspended in 30 % Matrigel) and tumor volume is evaluated using a phlethysmometer twice a week for 30-60 days. Blood is drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data is expressed as the mean +/- SEM. Student's and Mann-Whitney tests are used to assess differences between means using the InStat software package. A COX-2 inhibitor and a topoisomerase II inhibitor are administered to the animals in a range of doses. Analysis of lung metastasis is done in all the animals by counting metastasis in a stereomicroscope and by histochemical analysis of consecutive lung sections.

HT-29 Model

[0372] Mice are injected subcutaneously in the left paw (1×10^6 tumor cells suspended in 30 % Matrigel) and tumor volume is evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of human colon cancer cells (HT-29) into nude mice produces tumors that reach 0.6-2 ml between 30-50 days. Blood is drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data is expressed as the mean +/- SEM. Student's and Mann-Whitney tests are used to assess differences between means using the InStat software package.

[0373] Mice injected with HT-29 cancer cells are treated with a topoisomerase II inhibitor i.p at doses of 50 mg/kg on days 5,7 and 9 in the presence or absence of celecoxib in the diet. The efficacy of both agents is determined by measuring tumor volume.

[0374] In a second assay, mice injected with HT-29 cancer cells are treated with a topoisomerase II inhibitor on days 12

through 15. Mice injected with HT-29 cancer cells are treated with a topoisomerase II inhibitor i.p at doses of 50 mg/kg on days 12, 13, 14, and 15 in the presence or absence of celecoxib in the diet. The efficacy of both agents is determined by measuring tumor volume.

[0375] In a third assay, mice injected with HT-29 colon cancer cells are treated with a topoisomerase II inhibitor i.p 50 mg/kg on days 14 through 17 in the presence or absence of celecoxib (1600 ppm) and valdecoxib (160 ppm) in the diet. The efficacy of both agents is determined by measuring tumor volume.

NFSA Tumor Model

[0376] The NFSA sarcoma is a nonimmunogenic and prostaglandin producing tumor that spontaneously developed in C3Hf/Kam mice. It exhibits an increased radioresponse if indomethacin is given prior to tumor irradiation. The NFSA tumor is relatively radioresistant and is strongly infiltrated by inflammatory mononuclear cells, primarily macrophages which secrete factors that stimulate tumor cell proliferation. Furthermore, this tumor produces a number of prostaglandins, including prostaglandin E_2 and prostaglandin I_2.

[0377] Solitary tumors are generated in the right hind legs of mice by the injection of 3 x 10^5 viable NFSA tumor cells. Treatment with a COX-2 inhibiting agent (6 mg/kg body weight) and a topoisomerase II inhibitor or vehicle (0.05% Tween 20 and 0.95% polyethylene glycol) given in the drinking water is started when tumors are approximately 6 mm in diameter and the treatment ia continued for 10 consecutive days. Water bottles are changed every 3 days. In some experiments, tumor irradiation is performed 3-8 days after initiation of the treatment. The end points of the treatment are tumor growth delay (days) and TCD_{50} (tumor control dose

50, defined as the radiation dose yielding local tumor cure in 50% of irradiated mice 120 days after irradiation). To obtain tumor growth curves, three mutually orthogonal diameters of tumors are measured daily with a vernier caliper, and the mean values are calculated.

[0378] Local tumor irradiation with single γ-ray doses of 30, 40, or 50 Gy is given when these tumors reach 8 mm in diameter. Irradiation to the tumor is delivered from a dual-source ^{137}Cs irradiator at a dose rate of 6.31 Gy/minute. During irradiation, unanesthetized mice are immobilized on a jig and the tumor is centered in a circular radiation field 3 cm in diameter. Regression and regrowth of tumors is followed at 1-3 day intervals until the tumor diameter reaches approximately 14 mm.

[0379] The magnitude of tumor growth delay as a function of radiation dose with or without treatment with a COX-2 inhibiting agent and a topoisomerase II inhibitor is plotted to determine the enhancement of tumor response to radiation. This requires that tumor growth delay after radiation be expressed only as the absolute tumor growth delay, i.e., the time in days for tumors treated with radiation to grow from 8 to 12 mm in diameter minus the time in days for untreated tumors to reach the same size. It also requires that the effect of the combined COX-2 inhibiting agent and topoisomerase II inhibitor plus-radiation treatment be expressed as the normalized tumor growth delay. Normalized tumor growth delay is defined as the time for tumors treated with both a COX-2 inhibiting agent and radiation to grow from 8 to 12 mm in diameter minus the time in days for tumors treated with a COX-2 inhibiting agent and a topoisomerase II inhibitor alone to reach the same size.

[0380] The contents of each of the references cited herein, including the contents of the references cited within

these primary references, are herein incorporated by reference in their entirety.

[0381] While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the active agents used in the methods, combinations and compositions of the present invention as indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.